CLINICO-PATHOLOGICAL STUDY OF PAEDIATRIC LIVER TUMORS

Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations
for the award of the degree of

M.Ch. BRANCH – V
PAEDIATRIC SURGERY

2007 – 2010

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN
MADRAS MEDICAL COLLEGE
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI

AUGUST - 2010

CERTIFICATE

This is to certify that the dissertation entitled **"Clinico-Pathological Study of Paediatric Liver Tumors"** is a bonafide work done by **Dr.A.Ravindar** under my guidance and supervision during the period between 2007 – 2010 towards the partial fulfillment of requirement for the award of M.Ch Branch V (Paediatric Surgery) degree examination held in August 2010 by The Tamilnadu Dr. M.G.R. Medical University, Chennai.

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DECLARATION

I solemnly declare that the dissertation entitled **"Clinico-Pathological Study of Paediatric liver tumors"** is the original work done by me at The Institute of Child Health & Hospital for Children, Egmore, during the M.Ch. course (2007 to 2010), under the guidance and supervision of Prof. S.V. Senthilnathan MS., M.Ch., Professor and H.O.D. of Paediatric Surgery. The dissertation is submitted to THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY towards the partial fulfillment of requirement for the award of M.Ch. (BRANCH – V) IN PAEDIATRIC SURGERY.

Place : Chennai **Dr. A.RAVINDAR**

Date : 26th May, 2010

ACKNOWLEDGEMENT

It gives me immense pleasure to express my deep sense of gratitude to **Prof. S.V. Senthilnathan. MS., M.Ch.,** Prof. and H.O.D. of Paediatric Surgery, for his able guidance during the course of study and in preparation of this dissertation.

I sincerely thank **Prof. P. Mohan MS., M.Ch.,** and **Prof.K.Saravanabavan**, **MS., M.Ch.,** for helping me to complete this dissertation.

I sincerely thank my former H.O.D. **Prof.P.Jayakumar**, and **Prof.S.Philip Chandran** for their constant encouragement and support in completing the study.

I express my thanks to Assistant Professors **Dr.R.Senthilnathan, Dr.S.R.Reghunandan, Dr.J.Krishnamohan, Dr.V.Giridharan, Dr.D.Vembar, Dr.R.Velmurugan, Dr.C.Sankkarabarathi, Dr. S. Kasi, Dr. G. Hariharan, Dr.J.Muthukumar, Dr.Mohankumar,** and **Dr.C.Saravanan** for their encouragement during the course of study.

I sincerely thank **Dr. C. Natarajan** Department of Radiology, **Prof. T.B. Uma Devi, Dr.Selvambigai** and **Dr.Jaiganesh** Department of Pathology, **Prof. Kalaiselvi** and **Dr. Rajasekar** Department of Medical Oncology and **Dr. R. Vijayalakshmi,** Department of Radio Therapy, Institute of Child Health, Chennai for helping me to complete this study.

I thank **Prof. Saradha Suresh M.D., Ph.D,** Director and Superintendent, Institute of Child Health & Hospital for Children, Egmore, for permitting me to use all resources for my dissertation work.

I thank my family members for their support towards completing my study successfully. Last but not the least, I heartily thank the patients and their parents for their kind support and cooperation for successful completion of this study.

CONTENTS

INTRODUCTION

Primary neoplasms of the liver occur rarely during childhood and constitute only 0.3-2% of all pediatric tumors [1]. However, they comprise a variety of entities including benign and malignant epithelial, as well as mesenchymal tumors, the most common of these being hepatoblastoma. Other malignant liver tumors are quite rare and include biliary rhabdomyosarcoma, angiosarcoma, rhabdoid tumor, and undifferentiated sarcoma [2]. The commonly seen benign liver tumors in children are infantile hemangioma, mesenchymal hamartoma, and focal nodular hyperplasia. Rare benign tumors are hepatic adenoma and teratoma [2]. Clinical presentation, especially in young children is relatively uniform with abdominal enlargement and a painless tumor, and often specific symptoms develop late. Prerequisites for clinical diagnosis are a comprehensive laboratory workup and good quality imaging mainly with ultrasound, as well as CT and/or MRI scans. Histological diagnosis is essential for differential diagnosis. Major progress has been achieved during the last decades in the treatment of malignant liver tumors in children, both in chemotherapy and in surgical management [3]. Surgery is the mainstay of treatment for all benign and malignant liver tumors [1]. Prognosis nowadays usually is good in all benign tumors and hepatoblastoma, as well as in some other rare malignancies, but dismal in hepatocellular carcinoma and other chemotherapy non sensitive malignant tumors. The future in the treatment of children with advanced malignant liver tumors lies in primary liver transplantation.

AIM OF THE STUDY

1. To study the incidence and age distribution of various liver tumors in children.

2. To study the mode of presentation and clinical profile of both benign and malignant liver tumors.

3. To study the role of tumor markers and imaging techniques in the preoperative workup of these tumors.

4. To study the role of primary liver resections in achieving disease free survival.

5. To assess the effectiveness of adjuvant and neoadjuvant chemotherapy in downstaging the disease.

6. To study the outcome based on morbidity and mortality profile of the children treated within the period of study.

7. To identify pitfalls (if any) in the management protocol to improve the long term survival.

8. To suggest guidelines for future management.

REVIEW OF LITERATURE

EPIDEMIOLOGY

The liver is the third most common site for intra-abdominal malignancy in children, following adrenal neuroblastoma and Wilms tumor [4]. Two thirds of liver tumors in children are malignant [1]. Unlike liver tumors in adults, where the predominant histology is hepatocellular carcinoma, hepatoblastoma accounts for two thirds of liver tumors in children.

Hepatoblastoma is associated with Beckwith-Wiedemann syndrome, familial adenomatous polyposis, hemihypertrophy and low birth weight [5][6][7][8][9]. The most common genetic aberrations involve chromosomes 1p, lq, 2q, 4q, 7q, 8q, 12p, 17q, 20, 22q, Xp, and Xq [10][11][12]. Hepatoblastoma has been associated with stabilizing mutations of beta-catenin and activation of Wnt/beta-catenin signaling [13]. Up-regulation of insulin-like growth factor 2 has also been observed in hepatoblastoma [14]. VLBW infants are also at a higher risk of developing advanced hepatoblastoma [15]. The cause of hepatoblastoma remains unclear, but recent theories suggest that hepatoblastoma is derived from a pluripotent hepatic stem cell or oval stem cell that can differentiate into both hepatocytes and biliary epithelial cells.

Hepatocellular carcinoma occurs predominantly in the setting of underlying liver disease due to hepatitis B virus and cirrhosis. In young children, hepatocellular carcinoma has been associated with tyrosinemia and other inherited metabolic disorders [16].

One third of liver tumors are benign. Benign tumors of the liver in children include vascular tumors, hamartomas, adenomas, and focal nodular hyperplasia. Benign liver tumors interestingly tend to occur in patients with other conditions. Hepatic adenomas have long been associated with the use of oral contraceptive pills in adults [17]. Children are at risk for hepatic adenomas when they have received androgen therapy for aplastic anaemia, have chronic iron overload from transfusion in beta-thalassemia, or have received corticosteroids after renal transplantation [18]. Patients with type 1 glycogen storage disease are at increased risk for hepatic adenoma [19] and focal nodular hyperplasia [20]. Liver hamartomas may occur in children with tuberous sclerosis [21].

Other liver malignancies in children include sarcomas, germ cell tumors and rhabdoid tumors. The histology and anatomy of a pediatric liver tumor guides the treatment and prognosis.

CLINICAL PRESENTATION

There exists a relatively typical distribution of liver tumors in different age groups, which are however, not totally exclusive, since

rarely typical tumors of infancy have been observed in adults and vice versa. The age distribution and relative frequency are shown below in table1 [1]:

Table 1 Primary pediatric liver tumors, their age distribution, and relative frequency in Western countries (other tumors <1%)

Age Group	Malignomas	Benign Tumors
Infants, toddlers	hepatoblastoma (43%) rhabdoidtumor (<1%) mal. germ cell tumors (<1%)	vascular tumors (14%) mes. hamartoma (6%) teratoma (<1%)
School age, adolescents	hepatocellular carcinoma (23%) sarcomas (7%)	adenoma (2%) FNH (2%)

mes, mesenchymal; FNH, focal nodular hyperplasia.

Most children with a primary liver tumor present with abdominal distention and a palpable mass often without other signs of severe disease [22][23]. Anemia is often present. Only in advanced stage of the disease, the overall status deteriorates and the children develop abdominal pain, weight loss, nausea, vomiting, ascites, and in case of pulmonary metastases progressive respiratory problems. Jaundice, signs of hepatic insufficiency or an incidental rupture of the tumor with intraabdominal bleeding are very rare. Thus, many tumors reach a considerable size before treatment can be initiated. However, some specific symptoms are associated with the different tumors, such as fever and thrombocytosis with hepatoblastoma and precocious puberty secondary to human chorionic gonadotropin (HCG) or rarely testosterone production in hepatoblastoma or germ cell tumors. High output cardiac insufficiency due to arterio-venous shunting in the tumor and platelet sequestration and consumptive coagulopathy (Kasabach-Merritt syndrome) can be

encountered in young infants with a hemangioma or hemangioendothelioma of the liver, who often also show hemangiomas of the skin and other organs.

LABORATORY INVESTIGATIONS

ROUTINE BLOOD INVESTIGATIONS

Routine laboratory tests should include Complete blood counts, C-reactive protein, transaminases, glutamyl transferase, alkaline phosphatase, and bilirubin in all patients. Virological titers for hepatitis A, B, and C, HIV-1and EBV should be done in suspected cases of hepatocellular carcinoma. Thrombocytosis is present in 60% of cases [24].

TUMOR MARKERS

The most important and sensitive laboratory test for hepatoblastoma and hepatocellular carcinoma is serum AFP level, because it is highly elevated in over 90% of all hepatoblastoma and moderately elevated in 70% of Hepatocellular Carcinoma patients [25][26]. It can also be highly elevated in malignant teratoma and yolk sac tumors of the liver. Slightly elevated levels may also be found in other tumors, as well as after damage or during regeneration of liver parenchyma. Falsely elevated serum AFP levels can be noted in hepatitis, cirrhosis, hemangioendothelioma, germ cell tumor, testicular tumor and

gallbladder carcinoma. Normal AFP levels have been observed with both well-differentiated and immature hepatoblastomas and frequently occur with the fibrolamellar variants of hepatocellular carcinoma [25][27][28]. Normal AFP level in hepatoblastoma indicates that these tumors are biologically more aggressive [29][30]. Serum AFP levels can be used to monitor chemotherapeutic efficacy and to detect disease recurrence. AFP levels must be interpreted with caution in children as there is a wide range of AFP in the first years of life, with normal levels exceeding 500,000ng/ml in neonates and 300 ng/ml in 3 year old children.

The other tumor markers of liver include:

HCG	hepatoblastoma, malignant germ cell tumors.
Testosterone	hepatoblastoma.
Ferritin	Hepatocellular carcinoma.
CEA	Hepatocellular carcinoma.
LDH	many malignant tumors.
NSE, catecholamines	liver infiltration by neuroblastoma.

Rarely, a Hepatoblastoma secreting Beta-HCG is associated with sexual precocity.

IMAGING

Imaging is helpful both for diagnostic purposes and to assess tumor resectability. Ultimately, imaging should delineate the size and location of tumors, evaluate for metastastic disease, and determine whether vascular invasion of the portal vein, hepatic veins, or inferior vena cava is present. Although advances in imaging have improved the ability to predict resectability, the ultimate assessment is made in the operating room by the surgeon.

ULTRASOUND

The best and easiest technique for imaging of suspected tumor in the liver is ultrasound, which can be used repeatedly without anesthesia even in young children. With this technique, a tumor can be clearly localized to the liver and its internal structure can be detected [1]. Ultrasonography is helpful for the initial evaluation to assess vascular involvement. Doppler ultrasonography is helpful in identifying the tumor's relationship to neighboring vessels and in diagnosing venous thrombosis and vascular shunts within the tumor [31]. Malignant liver neoplasms are usually well-defined hyperechoic (solid) lesions on ultrasonography [15]. It has also been used intraoperatively to aid in determining vascular involvement and tumor resectability.

CT AND MRI SCAN

The tumor type, size, location and borders of a liver tumor and its resectability can be better determined by CT or MRI scan, the latter giving better contrast between normal liver and neoplastic tissue [33]. With a combination of these techniques, the individual lesion can be identified as, either, solitary or multifocal, solid or cystic, with homogeneous or inhomogeneous internal structure. CT and MRI scans can also demonstrate invasion into vessels or extrahepatic structures and enlargement of lymph nodes. Liver tumors have homogeneous hypointensity on Tl-weighted images and hyperintensity on T2-weighted images [34]. Three-dimensional reconstruction can significantly enhance the surgeon's ability to predict resectability.

CONVENTIONAL ANGIOGRAPHY & MR ANGIOGRAPHY

Conventional angiography was used in the past to delineate the anatomy of the hepatic vasculature, but with the availability of MR Angiography planning of resection of tumors especially those with noncharacteristic features in imaging, such as malignant tumors with a completely homogeneous internal structure or hepatoblastoma presenting as a solitary cyst can be now done with ease. MR Angiography has made conventional angiography superfluous [35]. Angiography can still be used in some cases to perform selective chemoembolisation as a therapeutic intervention.

HEPATIC SCINTIGRAPHY

This helps in the identification of focal nodular hyperplasia with an increased 99m-Technetium-sulfur uptake in contrast to hepatic adenoma.

CT CHEST / CEREBRAL MRI / BONE SCAN

Aside from a conventional thoracic radiograph, a CT scan of the chest is essential to find or rule out pulmonary metastasis. In HCC it is necessary to expand imaging in search for metastases applying cerebral MRI as well as bone scan.

FDG PET SCAN

There has been very little experience with positron emission tomography in pediatric liver tumors. In combination with an MRI scan, PET scan is capable of localizing recurrent hepatoblastoma and HCC somewhat more precisely than MRI alone.

DIFFERENTIAL DIAGNOSIS AND HISTOLOGY

The ultimate diagnosis of the type of liver tumor is made with a biopsy and a histological examination is mandatory for all primary pediatric liver tumors either after an initial resection or before initiation of chemotherapy in unresectable cases. This can be done percutaneously, laparoscopically, or through the open approach. Fine needle aspiration can be sufficient for diagnosis and some even suggest that neoadjuvant

chemotherapy can be started on the basis of clinical features only [25]. Owing to the significant error rate in clinical diagnosis, a biopsy in all cases is strongly advocated by many [36].

NEEDLE BIOPSY

It is still a controversy, whether a needle biopsy is sufficient for a histological diagnosis. Some advocate that a cytological examination of needle aspiration can differentiate hepatoblastoma, hepatocellular carcinoma and benign lesions [37][38] but it is generally felt that needle biopsies are insufficient. Some consider that a Tru-cut needle biopsy permits sufficient histological workup, is simple with a low rate of complications and ideal for children with an unresectable tumor [39].

LAPAROSCOPY OR LAPAROTOMY AND BIOPSY

This is considered to be the most ideal as it offers the advantage of direct visualization of the liver tumor and therefore helps in taking a more representative sample from the lesion and at the same time it is possible for surgical assessment of resectability and also sample enlarged lymph nodes for accurate staging.

The distribution of the various malignant and benign primary hepatic tumors is shown in table 2:

Table 2

Incidence of Primary Hepatic Tumors in Childhood

Tumor	% of Patients
Malignant	
Hepatoblastoma	43
Hepatocelluar Carcinoma	23
Sarcoma	6
Benign	
Benign Vascular tumor	13
Mesenchymal Hamartoma	6
Adenoma	2
Focal nodular hyperplasia	2
Other	5

Hepatoblastoma and hepatocellular carcinoma are of epithelial origin and account for more than 90% of malignant liver neoplasms [40]. Primary liver neoplasms can also be of mesenchymal origin, of these, sarcomas are the most common (Undifferentiated embryonal sarcomas and Rhabdomyosarcoma). Other reported malignancies include the malignant transformation of mesenchymal hamartoma, angiosarcoma, cholangiocarcinoma, rhabdoid tumor, immature teratoma, and choriocarcinoma. Metastatic disease to the liver is relatively uncommon in children.

BENIGN TUMORS OF THE LIVER

Benign tumors may be epithelial (focal nodular hyperplasia, hepatocellular adenoma), mesenchymal (mesenchymal hamartoma), vascular (infantile hemangioendothelioma, cavernous hemangioma), or others (teratoma, inflammatory pseudotumor). The most common benign liver tumor in infants is hemangioma. Commonly seen benign tumors in toddlers are mesenchymal hamartoma and focal nodular hyperplasia. Hepatic adenoma is almost exclusively a disease of older children.

INFANTILE HEPATIC HEMANGIOENDOTHELIOMA

Infantile Hepatic Hemangioendothelioma (IHH) is the most common benign liver tumor in children. IHH is now being diagnosed prenatally, and similar to affected neonates, the fetus may be asymptomatic or profoundly ill [41][42]. Children with symptoms present before 6 months of age 80% of the time, with many presenting in the newborn period [42][43][44]. The most common finding on examination is hepatomegaly. The severity of the disease may vary from asymptomatic children to those with life threatening CHF, abdominal compartment syndrome, and severe thrombocytopenia. 50% of children have a cutaneous hemangioma also [44]. On ultrasonography, lesions appear as multifocal, echolucent nodules with high flow vessels or as solitary heterogenous echogenic lesions [45]. On a plain CT scan the lesions have a low attenuation and on contrast administration they

enhance diffusely or centripetally [45]. MRI reveals the extent of the disease, the flow characteristics, and the flow structure [45]. AFP and catecholamine levels should be obtained to rule out a hepatoblastoma or a stage 4S neuroblastoma [46].

Dehner and Ishak identified two types of IHH are Type 1, which is more common and is characterized by an orderly arrangement of dilated and compressed endothelium lined vascular spaces supported by reticulin fibres with benign cytologic features. Type 2 lesions have a more aggressive appearance with more complex and irregular branching structures within the vascular lumens.

The treatment depends upon the severity and the location of the lesion. If the child is asymptomatic with little hepatomegaly, observation is the appropriate therapy. Percutaneous or open biopsy is discouraged because of the risk of significant hemorrhage. In a symptomatic child pharmacological control with corticosteroids [42][43][44], interferon(IFN) [47][48], vincristine [49], or cyclophosphamide [50] should be tried. Embolisation is most effective in children with disease restricted to only a few segments. Although hepatic artery ligation was recommended in the past, it prevents effective embolisation and thus should be avoided. Hepatic resection or liver transplantation may be needed if disease progression occurs despite medical management [51].

HEMANGIOMA

Hemangioma is the most common benign liver tumor in adults; in children, however hemangiomas are usually incidental findings in asymptomatic patients [52]. Hemangiomas have widely dilated, nonanastamotic vascular spaces lined by flat endothelial cells and supported by fibrous tissue [52]. The natural history for hemangiomas is spontaneous regression in the first 2 years of life. Medical management consists of high-dose steroids (3-5 mg/kg/d) for 3-5 weeks. However, the response time is slow, and lesions can rebound once the drug is stopped. Focal lesions can be treated with complete surgical excision or with selective hepatic artery embolization. The overall prognosis for these benign hepatic tumors in children is good.

MESENCHYMAL HAMARTOMA

Mesenchymal hamartomas are the second most common benign liver tumor, comprising 5% of liver tumors in children [40]. They are known by various names including pseudocystic mesenchymal tumor, giant cell lymphangioma, cystic hamartoma, bile cell fibroadenoma and cavernous lymphangiomatoid tumor. The term mesenchymal hamartoma was coined by Edmondson in 1956 [53]. They are typically diagnosed when the patient is younger than 2 years. They can sometimes be seen on a prenatal ultrasound, but usually presents as an asymptomatic abdominal mass or after a period of rapid growth with compression of adjacent

tissues leading to vena caval compression, feeding difficulties, and respiratory distress secondary to upward pressure on the diaphragms. The right lobe is more commonly involved and on ultrasound or CT scan they have a pathognomonic appearance of a single large fluid filled mass with fine internal septations and no calcifications [54]. The AFP levels are usually normal but may be mildly elevated. Mesenchymal hamartoma usually follows a benign course [53] although there are reports of sarcoma arising from these lesions. The treatment of choice is complete surgical resection as lesions may recur with incomplete removal of the tumor.

FOCAL NODULAR HYPERPLASIA AND HEPATIC ADENOMA

Focal nodular hyperplasia (FNH) and hepatic adenomas are rarely seen in childhood. Both of these benign lesions have an association with a high estrogen environment and frequently occur in adolescent girls. Hepatic adenomas are associated with oral contraceptive use, type 1 glycogen storage disease [55].

A characteristic central scar on CT scan is pathognomonic for FNH. Unenhanced CT scans show a hypodense well-defined lesion. A 3-phase CT scan is the optimal study to make the diagnosis of FNH, including an arterial phase, portal venous phase, and delayed images. During the arterial phase, an FNH appears as an early contrast-enhanced homogenous lesion that becomes isodense with the normal liver

parenchyma on delayed images. Differentiating FNH from adenomas may require technetium sulphur colloid scan, which shows uniform uptake by FNH lesions. Open biopsy may be required for definitive diagnosis in rare circumstances.

FNH lesions have no malignant potential and are often asymptomatic. Elective resection may be done to prevent spontaneous rupture and hemorrhage or they can be followed up with serial US monitoring. If the lesions are symptomatic or rapidly enlarging, complete surgical resection, embolization, or hepatic artery ligation may be used for treatment.

Hepatic adenomas are treated with complete surgical excision because these lesions have a small risk for rupture, hemorrhage, or malignant transformation to hepatocellular carcinoma.

TERATOMA

Hepatic teratoma in children is very rare. These children are younger than 1 year, and calcification is usually present within the lesion. Serum AFP levels may only be mildly elevated in comparison to hepatoblastoma. Resection is the treatment of choice owing to risk of malignancy from any immature elements of the tumor.

INFLAMMATORY PSEUDOTUMOR

Inflammatory pseudotumor of the liver is rare. It is seen in children older than 3 years. Because it is predominantly solid, it is difficult to differentiate it from other benign or malignant tumors by imaging studies. Fever, leukocytosis, and high C-reactive protein level in a child with a solid liver mass and normal AFP level are suggestive of an inflammatory pseudo tumor. Because it is difficult to diagnose this lesion without a large biopsy or resection of the lesion, most children undergo resection, which is curative.

MALIGNANT TUMORS OF THE LIVER

HEPATOBLASTOMA

Hepatoblastoma (HB) is the most common primary hepatic malignancy in childhood, accounting for 43% of all pediatric liver tumors [1]. Hepatoblastomas are composed of cells resembling the developing fetal and embryonic liver, hence the classification as an embryonal tumor. Most commonly, these tumors present in the right lobe of the liver. Histologically, these tumors can be divided into epithelial or mixed epithelial/mesenchymal tissue. The epithelial type is subdivided into fetal, embryonal, macrotrabecular, and small cell undifferentiated types. The fetal histology carries the most favorable prognosis [56] and the Small cell undifferentiated the worst prognosis [29].

The typical presentation is a child younger than 3 years with an abdominal mass, anemia, failure to thrive, and vomiting. An increased risk of hepatoblastoma exists in association with hemihypertrophy, Beckwith-Wiedemann syndrome and familial adenomatous polyposis.

Associated laboratory abnormalities include an elevated AFP and thrombocytosis. More that 90% of patients with hepatoblastoma have elevated AFP levels and tumors that do not express AFP at diagnosis are felt to be biologically more aggressive [29][30]. Ultrasound identifies the liver as the organ of origin and the extent of tumor within the liver. Doppler evaluation can be used to evaluate the patency of the inferior vena cava, the hepatic veins, and the portal vein. CT scans of the abdomen and chest are used to assess resectability and evaluate for the presence of pulmonary metastasis. Hepatic angiography or MRI angiography is frequently helpful preoperatively to determine resectability because it delineates the vascular anatomy more precisely.

Cure from hepatoblastoma mandates a complete gross resection of the primary tumor at some point during the treatment regimen. Even though about half of the tumors can be resected by primary operation, preoperative chemotherapy should precede the operation in case of large tumors even when there is possibility of resection [58]. This strategy helps to preserve more mass of healthy hepatic tissue and decrease intraoperative and postoperative complications. If the tumor is unresectable at presentation (50% of tumors), then neo-adjuvant

chemotherapy is started before definitive resection. Even if unresectable at diagnosis, most hepatoblastomas are chemosensitive, especially to “platinum” containing chemotherapeutic agents and cisplatin remains the backbone of any chemotherapy regimen. Unresectability is largely due to the size of the tumor with attendant invasion of hepatic vessels and the inferior vena cava (IVC) [57]. Adequate response to chemotherapy is observed in 70% of patients who then go on to complete resection followed by additional postoperative chemotherapy. Orthotopic liver transplantation is an option in children with unresectable primary tumors and without demonstrable metastatic disease after neoadjuvant chemotherapy and pulmonary metastasectomy. AFP is considered an early marker for recurrence, and elevated levels should prompt thorough investigation.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is the second most common malignancy of the liver in children. Hepatocellular carcinoma (HCC) accounts for 23% [1] of pediatric hepatic malignancies and occurs in older children than hepatoblastoma. Predisposing conditions include hepatic fibrosis and cirrhosis secondary to metabolic liver disease, tyrosinemia, alpha 1 antitrypsin deficiency, type 1 glycogen storage disease, viral hepatitis (hepatitis B & C), primary sclerosing cholangitis,. Less commonly, HCC occurs in children without preexisting liver disease.

Patients with HCC typically present with abdominal pain caused by the large size of the lesion. Associated weight loss, anemia, and fever may also be present. Liver function tests are routinely elevated; the AFP is elevated in half of the cases. The fibrolamellar variant is rarely associated with cirrhosis and rarely produces AFP. Metastases usually occur in the lung and lymph nodes. More than 70% of these tumors are considered unresectable at the time of presentation and are relatively chemoresistant. Complete surgical resection or transplantation of localized disease is often the only hope. Multifocal tumors carry a very high relapse rate. New treatment modalities include metronomic chemotherapy and adjuvant anti-angiogenic therapy and are the target of investigation [59][60][61].

SARCOMA OF THE LIVER

Primary sarcoma of the liver is a rare entity. Undifferentiated (embryonal) sarcoma is an aggressive tumor with an unfavourable prognosis. Recent multimodal approaches has led to a reported survival of up to 70% of children [62][63]. Angiosarcoma of the liver is an aggressive malignant subtype with a poor prognosis. Sporadic case reports of malignant transformation of infantile hemangioma to angiosarcoma have been reported [64][65]. Embryonal or botryoid rhabdomyosarcomas arising from biliary ducts typically present with jaundice secondary to biliary obstruction and are known to have a favorable prognosis as they are chemo and radio sensitive. Rhabdoid

tumor of liver is an aggressive tumor seen in toddlers and school children and is chemoresistant and fatal.

HEPATIC METASTASES

Hepatic metastases in the pediatric population arise from a variety of primary malignancies, including neuroblastoma, Wilms tumor, rhabdomyosarcoma, rhabdoid tumor, non-Hodgkin lymphoma, adrenal cortical carcinoma, and osteogenic sarcoma. Current criteria for resection of these hepatic metastases include control of the primary tumor, a solitary or limited number of metastases, and a reasonable expectation of prolonged survival.

STAGING

Multiple staging systems have been proposed to classify both hepatoblastoma and hepatocellular carcinoma.

Pediatric Oncology Group (POG) staging system

The Pediatric Oncology Group (POG) in the United States uses a staging system based on the postoperative extent of disease. Although the POG staging system is useful in determining the postoperative prognosis, it does not provide information on the preoperative extent of disease. The staging is shown in table 3.

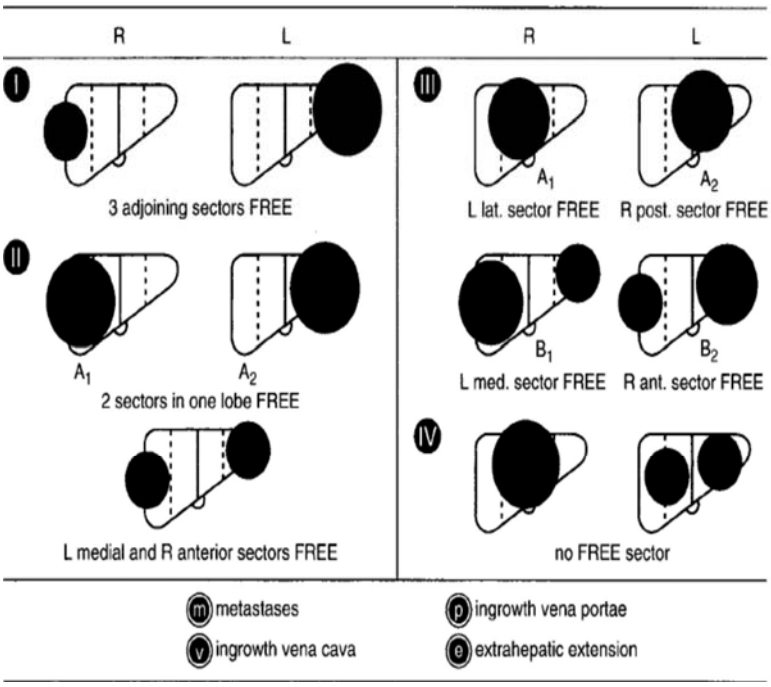
Table 3

Staging for Hepatoblastoma and Hepatocellular Carcinoma

Stage	Description
I	Complete resection
II	Microscopic residual tumor
III	Macroscopic residual tumor
IV	Distant Metastasis

PRETEXT (PRE Treatment EXTent of disease)

To describe the extent of the primary tumor, before and during therapy [66], the International Society of Pediatric Oncology (SlOP) developed the PRETEXT (pretreatment extent of disease) staging system. It also helps to assess tumor response and resectability before and after neoadjuvant chemotherapy, The PRETEXT system is based on radiologic findings and describes both the number and the location of involved liver sectors and takes into account invasion of the hepatic and portal veins as well as extrahepatic and metastatic disease. Imaging includes a spiral CT followed by contrast administration and/or MRI with gadolinium. This system has the advantage of being independent of therapeutic strategies and the individual surgeon’s judgment and therefore has very good reproducibility and an excellent predictive value as regards the prognosis [67][68].



The SIOP pretreatment grouping system (PRETEXT) describes the extent of liver involvement based on the number of sectors involved and takes into account metastasis (m), ingrowth of vena cava (v) and portal vein (p), and extrahepatic extension (e).

TREATMENT

SURGERY

The primary goal of surgery is complete anatomic resection of the tumor, both macro and microscopically which is of paramount importance in cure of liver cancers in children. Liver is one of the most difficult organs a surgeon can repair because of its friable tissue with an intricate network of ducts, veins and arteries. Major vascular structures, particularly the hepatic veins and inferior vena cava are prone to bleeding during resection. On the other hand, liver's regenerative capability and large functional reserve allow major resections of up to 80% of its tissue [69][70]. Successful hepatic resection requires careful planning and supportive care.

A sound knowledge of the three-dimensional segmental anatomy of the liver as described by Couinaud [71] as shown in figure, vascular occlusion techniques and expertise in performing different types of liver resections is essential for a successful outcome. Intraoperative ultrasound is useful in confirming the location of major vessels and other structures. Complete tumor resection can be easily achieved with a partial hepatectomy when the intrahepatic extent is limited to one or two sections (PRETEXT 1 & 2). When the tumor involves three sections (PRETEXT 3), preoperative neoadjuvant chemotherapy makes lesions considered “unresectable’ become resectable with a trisegmentectomy [1]. In centrally located lesions, resection of segments 4,5 & 8 (central hepatectomy) can be performed.

In general, nonanatomic, atypical liver resections should be avoided because of a higher rate of incomplete tumor resection, local relapse and postoperative complications [72].

Standard anatomic resections can lead to the loss of a significant percentage of liver parenchyma but most children with otherwise normal liver parenchyma can easily adapt to major resections with compensatory hyperplasia of the remaining liver within 3 months. The terminology used to define the anatomical limits of resection was given by Goldsmith and Woodburne and is shown in the table below along with the equivalent nomenclature in the Couinaud classification [86][87]:

Terminology of Goldsmith and Woodburne	Terminology of Couinaud
Right Hepatic Lobectomy	Right hepatectomy, segments V, VI, VII, VIII
Left Hepatic Lobectomy	Left hepatectomy, segments II, III, IV
Extended Right Hepatic Lobectomy	Extended right hepatectomy, segments IV,V, VI, VII, VIII, sometimes I
Extended Left Hepatic Lobectomy	Extended left hepatectomy, segments II, III, IV, V, VIII, sometimes I
Left Lateral Segmentectomy	Left lobectomy,, segments II, III
Central Hepatic Resection (Mesohepatectomy)	Segments IV, V, and VIII

Several instruments have been developed to help the surgeon minimize blood loss during dissection. These devices are welcome adjuncts to the basic techniques of finger fracture and electrocautery.

The Cavitron Ultrasonic Surgical Aspirator (CUSA®) is an innovative tool for resecting hepatic parenchyma, as it reduces intraoperative blood loss and perioperative morbidity and has become a standard surgical tool for liver resection. First introduced by Hodgson for liver surgery in 1984, it is a hand held instrument consisting of an acoustic vibrator, perfused with saline, which disrupts the liver parenchyma by producing a cavitational effect. CUSA®, combined with

bipolar cautery and a saline irrigation system, allows hepatic parenchyma resection in a bloodless manner. As the safety of liver resection depends mainly on the control of bleeding during parenchymal resection, the use of this technique has decreased morbidity in children undergoing major hepatic resections and specially those who have a smaller hepatic functional reserve.

The other adjuncts used to facilitate a bloodless parenchymal dissection include water jet dissection, argon plasma spray coagulation, Nd:YAG lasers, linear cutting staplers, LigaSure and Floating Ball apparatus by TissueLink.

ADJUVANT THERAPY

CHEMOTHERAPY

Although cure ultimately requires complete resection, cisplatin containing chemotherapy remains the mainstay of adjuvant therapy for hepatoblastoma and hepatocellular carcinoma. Neoadjuvant chemotherapy has been advocated by the SIOPEL group for childhood hepatoblastoma [66] for the purpose of downstaging the disease, improving the likelihood of complete resection, and ultimately improving long-term survival. Up to 50% to 70% of stage III hepatoblastomas can be rendered resectable after neoadjuvant chemotherapy [73]. The disadvantage of neoadjuvant therapy is that nonresponders can experience disease progression, and ultimately the tumor can be upstaged or become

unresectable. Prolonging chemotherapy beyond the total number of 6-8 courses, administered every 3 weeks, is unlikely to result in an unresectable tumor becoming resectable and Orthotopic Liver Transplantation (OLT) should be considered early. The commonly used drugs include cisplatin, vincristine, 5-fluorouracil and doxorubicin.

RADIOTHERAPY

Radiation therapy has a limited role in the management of hepatoblastoma and hepatocellular carcinoma. Current cooperative trials provide for permissive use of radiation therapy in children with residual disease. However, the ultimate goal remains complete surgical resection as the only effective means of cure.

ABLATIVE THERAPIES

Patients with lesions that cannot be anatomically resected and those who are not candidates for transplantation can be considered for local ablative therapies. These include chemoembolization, radiofrequency ablation, percutaneous injection of ethanol, and cryoablation. Ablative therapies offer palliation and may prolong survival but rarely achieve a cure. Alternatively, ablative therapies can act as a bridge to transplantation until a suitable donor becomes available.

NOVEL THERAPIES - SUICIDE GENE THERAPY [74].

This strategy was developed in the hope of avoiding the systemic side effects of standard adjuvant therapies. It involves the expression of a gene that converts a membrane permeable nontoxic prodrug into a toxic agent (suicide drug) in the tumor cells only and therefore causing destruction of the tumor cells only.

LIVER TRANSPLANTATION

Ultimately, up to 6% of patients with hepatoblastoma will require orthotopic liver transplantation [6][75]. The SIOPEL guidelines [76] for early referral for liver transplantation include:

i. Multifocal PRETEXT 4 hepatoblastoma.

ii. Large, solitary PRETEXT 4 hepatoblastoma, involving all four sectors of the liver, as confirmed by imaging. Unless tumor downstaging is cleary demonstrated after preoperative chemotherapy, as may be the case when the anatomical border of an uninvaded liver sector is compressed without true malignant invasion, primary liver transplant seems to be the best option.

iii. Unifocal, centrally located tumors involving main hilar structures or main hepatic veins, which would not become free of tumor even after an overall good response to chemotherapy and therefore not amenable to partial hepatectomy.

An absolute contraindication to liver transplantation is the persistence of extrahepatic deposits not amenable to surgical excision following chemotherapy.

In patients who undergo primary liver transplantation for hepatoblastoma following neoadjuvant chemotherapy, 10-year survival rates of 85 % have been reported [77]. Tumor recurrence is more frequent in children with a previous attempt at hepatic resection. In patients who undergo "rescue" liver transplantation following partial hepatectomy, the 5-year overall survival is 30% to 50%. Positive margins after an initial attempt at resection is associated with a poor prognosis. Therefore heroic attempts at partial hepatectomy should be avoided, and liver transplantation should be considered when the potential for complete resection is in question [77].

For hepatocellular carcinoma, liver transplantation has the theoretical advantage of removing not only the tumor but also the entire diseased preneoplastic liver. The scarcity of cadaveric donors, especially in the pediatric age group, has led to the use of segmental grafts from living donors or split-liver cadaveric donors. Living, related donor transplantation for tumors has been associated with improved graft survival and outcome [40]. Disadvantages of transplantation include the associated expense and risks of lifelong immunosuppression, which may enhance tumor recurrence or secondary malignancies.

Primary Orthotopic Liver Transplant (OLT) promises to be the future for children with advanced liver tumors not amenable to liver resections.

MATERIALS AND METHODS

This study on liver tumors in children is based on 34 patients admitted to the Institute of Child Health and hospital for children [ICH & HC], Egmore during the period from January 2005 to December 2009. The study includes 24 boys and 10 girls between the age group 6 days to 9 years. Data collected for each patient had been recorded in the enclosed chart.

- The body weight at presentation was documented in all cases. All the 34 children underwent a detailed analysis of symptoms and a thorough clinical examination before management.

- Antenatal history was documented in children presenting in the newborn period and findings of the antenatal scans were documented.

- All children underwent the routine panel of blood investigations like complete blood counts, renal function tests and liver function tests.

- Coagulation profile (prothrombin time, activated partial thromboplastin time, INR), was documented in all children before surgery or biopsy.

- A routine skiagram and CT scan of the chest was taken to document the pulmonary status of the patient.

- The diagnosis of liver tumor and the possible pathological type was based on imaging studies. Ultrasound abdomen was the initial baseline study done to confirm the anatomic origin and extent of the tumor. The presence or absence of ascites, lymph nodes and the involvement of vascular structures like the portal vein, hepatic veins and IVC was also noted. Duplex and colour Doppler ultrasonography was used to document a prominent hepatic artery, portal vein and arteriovenous shunting in hemangioendothelioma. Ultrasound abdomen was also used to follow up patients during preoperative chemotherapy and in the post operative period to document the response and to identify any local recurrence.

- Contrast enhanced CT scan was mandatory in all patients before neoadjuvant chemotherapy or liver resection, to better delineate the anatomy, the extent of the tumor and to plan the extent of resection preoperatively.

- MR Imaging was done in 1 patient with hemangioendothelioma, presenting as a huge abdominal mass in the newborn period.

- The most important investigation in the preoperative workup was tumor markers. Alpha feto protein(AFP) and beta HCG were done

in all patients. These were also used in the follow up period to document recurrence and disease progression.

- The diagnosis was confirmed by tissue biopsy in all but 3 cases of malignant liver tumor (hepatoblastoma), where the AFP was hugely elevated, prior to liver resection or neoadjuvant chemotherapy. In cases where imaging and tumor markers was suggestive of a benign tumor like hepatic adenoma, a liver biopsy was avoided prior to treatment.

- All children were registered with the Tumor Board at ICH and the treatment strategy was discussed extensively by a panel consisting of the paediatric surgeon, medical oncologist and pathologist. Parents were also involved in the process of decision making.

- The PRETEXT system of staging was used for malignant tumors prior to neo adjuvant chemotherapy.

- Children with unilobar resectable tumors were taken up for primary liver resection. Children with a large primary tumor and bilobar involvement were considered unresectable and were given neoadjuvant chemotherapy prior to surgical resection. Since ours is an institution with many consultants, hepatic resections were performed by different surgeons.

- Before surgical removal of the tumor, blood counts and parameters including the coagulation profile were confirmed to be within normal limits.

- Children were kept nil by mouth for 6 hours prior to the surgery. The incision was planned and marked out. General anaesthesia (ETGA) with epidural analgesia was administered in all patients. Central venous access was secured prior and arterial pressure monitoring was done in all patients during the surgical procedure. Bladder was catheterized using foley catheter to monitor the output. At laparotomy the resectability and tumor extent was assessed prior to mobilization of the liver. Portal dissection and vascular control was achieved before parenchymal dissection. Parenchymal dissection was carried out with thermal cautery and the finger fracture technique. Perfect hemostasis was secured prior to wound closure. Intraoperative blood losses were replenished with fresh whole blood or packed cells.

- All children were intensively monitored at the surgical ICU for stability of vital parameters. Pain relief was provided via the epidural catheter. The blood sugar, renal and liver function tests were monitored in the postoperative period. Children were shifted out of ICU to the general ward on the 5^{th} or 6^{th} post operative period, depending upon the general condition.

- Chemotherapy was given to all children with malignant liver tumors only. Chemotherapeutic schedule and drug dosing for malignant liver tumors was tabulated at the tumor board meet in consultation with the medical oncologist. All chemotherapeutic schedules were platinum based. The regimens followed were:

HEPATOBLASTOMA	VPF
MALIGNANT MESENCHYMOMA	PVC
ENDODERMAL SINUS TUMOR	BEP
EMBRYONAL SARCOMA	PA
V – vincristine, P – cisplatin, F – 5fluorouracil, B – bleomycin, E – etoposide, A – adriamycin, C – cyclophosphamide.	

VPF, PVC, PA were given in a once in 21 days cycle up to a maximum of 8 cycles depending upon the response. BEP regimen consisted of 6 weekly doses of bleomycin and 4 cycles of EP every 21 days. Blood counts were closely monitored before and after chemotherapy. Parents were counseled on the possible side effects of chemotherapy and the need to be compliant for every cycle. The drug dosage was as follows:

CISPLATIN	100 mg/m2 in divided doses for 3 days
VINCRISTINE	1.5mg/m2 per day
5 – FLUOROURACIL	600mg/m2 per day
ADRIAMYCIN	40mg/m2 in divided doses for 2 days
BLEOMYCIN	15-20U/m2/week for 5 weeks
ETOPOSIDE	100mg/m2/day for 3 days
CYCLOPHOSPHAMIDE	1 gram/m2 in divided doses for 3 days

Chemotherapeutic schedule for patients with recurrent disease was

CISPLATIN	100 mg/m2 in divided doses for 3 days
ADRIAMYCIN	40mg/m2 in divided doses for 2 days

Benign liver tumors did not warrant any chemotherapy.

- ❖ Follow up of patients who completed chemotherapy after surgery (n = 8) with the tumor board is as follows:

1	Monthly visits for 1 year	Blood counts, USG abdomen, AFP
2	3 monthly visits (total of 6 visits)	1+CXR
3	6 monthly visits for 1 year	1+2
4	Yearly visits thereafter	1+2

Patients on chemotherapy after surgery (n = 1) have blood counts, abdominal sonography and tumor markers prior to every cycle of chemotherapy and CXR at 3 monthly intervals till they complete chemotherapy. Once chemotherapy is completed the follow up is as shown above.

Patients with recurrent disease (n = 3) during follow up undergo CT scan of abdomen and chest in addition to other investigations and are started on the schedule for recurrent disease.

Children who completed chemotherapy after liver resection were also closely monitored during follow up for weight gain, achievement of normal developmental milestones, scholastic performance and for maintenance of normal liver function with adequate regeneration of the remnant liver.

OBSERVATIONS

This study conducted at ICH & HC is a prospective cum retrospective study done between January 2005 and December 2009 and it encompasses a total of 34 children admitted to the hospital with liver tumors both benign and malignant. The total number of boys was 24 (71%) and the total number of girls was 10 (29%). The youngest age at presentation was 6 days and the oldest child was 9 years. The mean age was 3 years.

Of the 34 children in the study, 33 children were symptomatic at presentation. The most common presenting symptom was mass in the abdomen (44%) noted by the parents. Abdominal distension was the next common complaint (41%). One third of the children has abdominal pain as their primary complaint and localized most commonly to the right hypochondrium. Jaundice was the presenting complaint in one patient at 40 days of life and was incidentally found to have a hemangioendothelioma on abdominal sonography. Nonspecific complaints like fever, loss of appetite and weight were noted in 9 children (26%).

Three children presented to us in the neonatal period and ante natal diagnosis with ultrasound was possible in 2 neonates with infantile hemangioendothelioma resulting in early diagnosis and treatment.

Hepatomegaly with a palpable firm mass was the most consistent finding in majority of the children (94%) presenting with liver tumor. Pallor was noted in 16 (47%) patients and correlated with a fall in hemoglobin levels. None of the 34 children demonstrated thrombocytopenia or congestive cardiac failure, especially those with infantile hemangioendothelioma where the kasabach merritt syndrome is a known association.

Chest X Ray and CT chest taken on initial presentation was normal in all children with malignant liver tumors under the study.

Liver function tests (serum bilirubin, SGOT, SGPT) were normal in all the patients except for the 1 child with infantile hemangioendothelioma, where the total bilirubin was elevated.

Tumor markers:

a. AFP – found to be elevated in 80% of patients with hepatoblastoma (16/20) and both patients with germ cell tumor. 20 % of children with hepatoblastoma (4/20) had normal AFP levels on presentation. Levels of AFP were normal in all other patients with other hepatic tumors. The AFP levels on follow up was found to be elevated in 3 patients (2 hepatoblastoma and 1 germ cell tumor), correlating with disease recurrence.

b. Beta HCG – was found to be normal in all patients with liver tumors.

ABDOMINAL IMAGING:

❖ ULTRASONOGRAPHY

USG was the basic initial imaging done to identify the organ of origin and extent of the tumor.

- ✓ In children with Hepatoblastoma the lesion was identified as a well defined, heterogenous or hypoechoeic lesion. Calcification within the tumor was noted in 2 cases of the mixed histological subtype. Thrombus in the portal vein branches was identified in 2 patients with hepatoblastoma. Endodermal sinus tumor was reported as hepatoblastoma.

- ✓ The USG of the child with embryonal sarcoma showed a cystic multi septated lesion from the right lobe of liver.

- ✓ Mesenchymal hamartoma classically appeared as a large, multilocular, cystic mass with internal septation without calcification in all the 5 children with this type of tumor.

- ✓ Hemangioendothelioma was seen as a heterogenous lesion with focal areas of increased echogenicity and prominent hepatic artery and portal vein on duplex and color Doppler. But the diagnosis had to be confirmed by an MRI in one of the 3 children with this tumor.

❖ CONTRAST ENHANCED CT SCAN OF ABDOMEN

- ✓ Hepatoblastoma presented as a homogenous or heterogenous lesion with peripheral rim enhancement classically seen in the mixed subtype. CT was able to better delineate the extent of involvement of lobes, compression or displacement of adjacent organs, status of lymph nodes, ascites and involvement of the portal vein and IVC. This information was very useful in planning the surgical procedure without any intra-operative surprises.

- ✓ Embryonal sarcoma was identified as a hypodense septate lesion with rim enhancement. But the USG and CT findings had to be correlated with tumor markers in a retrospective manner for accurate histological diagnosis.

- ✓ Mesenchymal hamartoma was seen as a large, multilocular, cystic mass with internal septation without calcification.

- ✓ Definite diagnosis of Hepatic adenoma was not possible as the lesion appeared as a nonspecific solitary, hypodense, non-enhancing lesion.

❖ MAGNETIC RESONANCE IMAGING:

- ✓ MRI was specifically useful in one child with infantile hemangioendothelioma and was seen as a large hypointense lesion on T1 and mixed intense lesion on T2 weighted images.

STAGING

The staging was done using the PRETEXT staging system and stage 2 was the most commonest and the remaining cases were stage 4 disease.

HISTOPATHOLOGY:

The percentage of malignant liver tumors in the study was 74% (25/34). The percentage of benign tumors was 26% (9/34). The most common malignant liver tumor was hepatoblastoma [80% (20/25)]. Of the 20 cases, 7 were of the fetal subtype, 3-embryonal, 2-macrotrabecular, 1-anaplastic and 7 were of the mixed histological subtype. The most common benign liver tumor was mesenchymal hamartoma [56% (5/9)]. There were no cases of hepatocellular carcinoma, hemangioma, rhabdomyosarcoma in the study. The distribution of the different tumors is shown in the bar diagram.

MALIGNANT	Hepatoblastoma	20
	Malignant mesenchymoma	1
	Endodermal sinus tumor	2
	Undifferentiated Embryonal sarcoma	1
	Secondaries liver	1
BENIGN	Mesenchymal hamartoma	5
	Infantile hemangioendothelioma	3
	Hepatic adenoma	1

TREATMENT

SURGICAL MANAGEMENT

- As noted above, of the 34 children studied, 25 had a malignant tumor and 9 had a benign tumor.
- Of the 25 children with a malignant tumor, 17 underwent liver resection.
- Of the 9 children with a benign tumor, 7 underwent surgical removal of tumor.
- Right hepatectomy (removal of segments 5,6,7,8) was performed in 14 children with right lobe tumor [9-hepatoblastoma, 1-infantile hemangioendothelioma, 2-mesenchymal hamartoma, 1-malignant mesenchymoma, 1-embryonal sarcoma].
- Left hepatectomy (removal of segments 2,3,4) was performed in 3 children with left lobe tumor [all 3 for hepatoblastoma].
- Wedge resection (removal of tumor with a margin of normal liver) was done in 3 patients [1-hepatic adenoma, 1-hepatoblastoma, 1-endodermal sinus tumor].
- Total excision of tumor alone was done in 4 patients [3-mesenchymal hamartoma, 1-endodermal sinus tumor].

		MALIGNANT (n=17)	BENIGN (n=7)
SURGERY (n=24)	RIGHT HEPATECTOMY	11	3
	LEFT HEPATECTOMY	3	0
	WEDGE RESECTION	2	1
	TOTAL EXCISION	1	3

TUMOR BIOPSY ONLY: 7 of the 25 children with malignant tumors had advanced disease at presentation and underwent only a biopsy to confirm the diagnosis.

CONSERVATIVE MANAGEMENT: 3 of the 34 children were managed conservatively [2-hemangioendothelioma which resolved spontaneously, 1-secondaries from neuroblastoma].

CHEMOTHERAPY

❖ **NEOADJUVANT CHEMOTHERAPY**

8 of the 17 children who underwent surgery for a malignant liver tumor had neoadjuvant chemotherapy. 1 child died in the immediate postoperative period due to hypovolemic shock.

❖ ADJUVANT CHEMOTHERAPY

9 of the 17 children underwent primary liver resection before adjuvant chemotherapy. 3 died in the immediate post operative period due to hypovolemic shock.

CHEMOTHERAPY (n=17)	NEOADJUVANT	8
	ADJUVANT	9

OUTCOME

- ✓ The outcomes of this study are based on follow up data documented with the ICH tumor board and data collected by contacting parents through telephone or by postcards dispatched to their residence.
- ✓ The follow up period ranges from 2 months to 5 years with a mean follow up period of 3 years.
- ✓ 16 of the 24 children who were operated (67%) are alive and are on regular follow up.
- ✓ 56% (9/16) of those on regular follow up have survived a malignant liver tumor [7-hepatoblastoma, 1-malignant mesenchymoma, 1-endodermal sinus tumor].

- ✓ The growth pattern and developmental milestones were similar to healthy children. The liver function tests were normal on follow up in all children who survived the disease and their ultrasonogram showed adequate compensatory hypertrophy of the remaining liver with no recurrence of the disease. Children who were of the school going age were found to have a normal scholastic performance and there were no drop outs.

- ✓ Children operated for benign tumors are all alive and there has been no mortality or disease recurrence in this group.

- ✓ Tumor recurrence after surgery occurred in 3 of the patients. These include wedge resection for hepatoblastoma and endodermal sinus tumor, right hepatectomy for undifferentiated embryonal sarcoma.

- ✓ Neoadjuvant chemotherapy is advantageous in terms of reduction in tumor size and therefore easier tumor handling and less per operative blood loss. Only one patient died in the immediate post operative period due to hypovolemic shock.

- ✓ On the contrary 3 deaths were noted with the adjuvant chemotherapy group were due to difficulty in handling a large tumor at primary liver resection leading to massive intra-operative blood loss or IVC tear.

DISCUSSION

Liver tumors, one third of which are benign, constitute 1.1% of childhood tumors [40]. The management of liver tumors in children has undergone a paradigm shift over the last 30 years. In the past decades, there were reservations to the use of chemotherapy in patients especially before surgery owing to the belief that chemotherapy was likely to adversely affect intra and post operative outcomes [66]. Another long held myth was that heroic liver surgery was the key to successful management. Improvements in radiological imaging, advances in the understanding of chemotherapy, improved surgical technique of liver resection, and the advances in paediatric liver transplantation have contributed to the favorable, outcome, of children afflicted with liver tumors.

In this study at ICH & HC, we had 34 patients in all, presenting with liver tumors and it includes both benign and malignant lesions. Since ours is an institution with many different consultants, liver resections were done by more than one surgeon. The data collected has been analyzed and compared to the world literature.

AGE AND SEX DISTRIBUTION

The age distribution of the various pediatric liver tumors as per Von Schweinitz D [1] is shown in table 1:

Table 1 Primary pediatric liver tumors, their age distribution, and relative frequency in Western countries (other tumors <1%)

Age Group	Malignomas	Benign Tumors
Infants, toddlers	hepatoblastoma (43%) rhabdoidtumor (<1%) mal. germ cell tumors (<1%)	vascular tumors (14%) mes. hamartoma (6%) teratoma (<1%)
School age, adolescents	hepatocellular carcinoma (23%) sarcomas (7%)	adenoma (2%) FNH (2%)

mes, mesenchymal; FNH, focal nodular hyperplasia.

In the youngest children, infants and toddlers, most malignant tumors are hepatoblastomas [1]. In older children the most common primary malignant liver tumor is hepatocellular carcinoma [2]. Tumors in intermediate age children, with features of both hepatoblastoma and HCC have been described as transitional cell tumors [78]. In the Indian context, in a study done by Minu Bajpai et al the age for hepatoblastoma varied from 16-38 months and the male female ratio was 1.5:1 [79]. In our study, there were a total of 24 boys and 10 girls.

The age and sex distribution of various malignant liver tumors is shown in the bar diagrams.

ANALYSIS OF SYMPTOMS IN COMMON LIVER TUMORS

ICH & HC is a government run institution and caters to the children belonging to the lower socio economic strata. Majority of parents of children with liver tumors are illiterate and ignorant of even the common paediatric problems. This is one of the reasons why a good number of our patients in the study presented to us in the advanced stage of the disease.

Most of our children presented with a mass in the abdomen or with abdominal distension, which was either noticed by the parents or by the referring physician. The following table compares the presenting complaints of the children in our study with the study done by Exelby PR et al [80].

MALIGNANT – HEPATOBLASTOMA		
	Exelby PR et al [80] %	**ICH & HC %**
MASS ABDOMEN	75	45
DISTENSION	23	45
PAIN	22	20
FEVER	Rare	25
WEIGHT LOSS	26	5
ANOREXIA	25	5
VOMITING	12	5
JAUNDICE	5	5

The most common benign tumor in our series was mesenchymal hamartoma. All children presented with abdominal distension. The table below compares the presenting complaints in our series with those of the study by Jonathan S K et al [81].

BENIGN – MESENCHYMAL HAMARTOMA		
	Jonathan S K et al [81] %	**ICH & HC%**
DISTENSION	100	100
VOMITING	50	20
PAIN	12.5	40
RESPIRATORY DISTRESS	12.5	NIL

ANTENATAL DIAGNOSIS

Primary liver tumors are very rare during the neonatal period, but increasing numbers of them are now diagnosed prenatally by routine ultrasound scan, therefore perinatal emergency situations can be avoided [83]. In our series, 2 children had antenatal scans suggestive of a hemangioendothelioma of the liver. One child was operated in the newborn period and the other had a spontaneous resolution of hemangioendothelioma on follow up.

TUMOR MARKERS

The most important tumor marker is the alpha-fetoprotein (AFP), because it is highly elevated in 80% to 90% of all Hepatoblastoma [1] and tumors which fail to express AFP at diagnosis are felt to be biologically more aggressive [29][30]. It has to be taken into account that it can also be highly elevated in malignant teratoma and yolk sac tumors

of the liver. Also important is the consideration of its wide range during the first years of life, with normal levels exceeding 500,000 ng/mL in neonates and 300 ng/mL in 3-year-old children [1]. Notably, most neonatal Hepatoblastomas do not produce enough AFP to produce serum levels markedly above the normal range. In our study at ICH & HC there were 4 children with hepatoblastoma (20%) with normal AFP (3-mixed subtype and 1-macrotrabecular subtype) and only one of the 4 has survived the disease.

HISTOPATHOLOGY:

The prognosis for liver tumors depends to a large extent on the histology of the tumor. Benign tumors have a uniformly good prognosis, and in our series of 34 children with 9 benign tumors there was no noted mortality. Histopathology of malignant tumors determines the response to treatment, thereby affecting the outcome, the fetal subtype of hepatoblastoma is a favourable histologic pattern [82] and was seen in 6 of our patients. The anaplastic subtype, was seen in 1 patient, who had advanced disease at presentation and did not respond to treatment. Mixed histology with mesenchymal component behaves in between the two and was found in 7 of our patients with hepatoblastoma.

In the study by Saniye Ekinci and Ibrahim Karnak et al [82] in 2006 from Turkey where 25 hepatic lobectomies were performed over 25

years, the histopathological distribution of tumors was as shown in the chart:

HISTOPATHOLOGICAL DISTRIBUTION	
Hepatoblastoma	11
Mesenchymal Hamartoma	5
Hepatocellular carcinoma	4
Hemangioendothelioma	1
Malignant mesenchymal tumor	1
Hemangioma	1
Metastases	1
Hepatic adenoma	1

In our study at ICH & HC over a period of 5 years, the distribution of tumors was akin to the one reported above. The most common malignant liver tumor was hepatoblastoma. We had no reported case of hepatocellular carcinoma in our series.

MALIGNANT	Hepatoblastoma	20
	Malignant mesenchymoma	1
	Endodermal sinus tumor	2
	Undifferentiated Embryonal sarcoma	1
	Secondaries liver	1
BENIGN	Mesenchymal hamartoma	5
	Infantile hemangioendothelioma	3
	Hepatic adenoma	1

TREATMENT

There are a wide range treatment options available for the management of liver tumors and these include liver resections, chemotherapy, radiotherapy, ablative therapies and liver transplantation. Hepatic resection is a fundamental treatment and is the gold standard for malignant and benign hepatic tumors of children and complete surgical removal of the tumor is the primary goal of any liver resection. Surgery of the liver has a special point in paediatric surgical practice. Liver is one of the most difficult organs a surgeon can operate upon because of its friable tissue with an intricate network of ducts, veins, and arteries. Major vascular structures, particularly the hepatic veins and inferior vena cava are prone to bleeding during resection. On the other hand, liver's regenerative capability and large functional reserve allow major resections of up to 80% of its tissue. Experience of surgeon, familiarity to complex hepatic anatomy and strict follow of anatomic planes directly affect results. Resection becomes more comfortable in cases with malignant liver tumors, which are initially treated by preoperative chemotherapy.

Benign liver tumors in childhood have long been associated with poor prognosis mostly due to surgical complications. Surgical treatment should be considered selectively in patients with benign liver tumors, especially with hemangiomas. Along with the technical advances in surgery and diagnostic tests, surgical treatment became feasible in benign

liver tumors of childhood in selected patients. In this series, 26% (9/34) of patients had benign tumors and total resection was possible in 7 without any morbidity or mortality.

The details of the hepatic resections from the study by Saniye Ekinci and Ibrahim Karnak et al [82] in 2006 from Turkey is shown below:

DETAILS OF HEPATIC RESECTIONS n = 25	
Right hepatic lobectomy	12
Left hepatic lobectomy	5
Extended left hepatic lobectomy	4
Extended right hepatic lobectomy	3
Enucleation of tumor	1

The details of hepatic resections at ICH & HC is as follows:

		MALIGNANT (n=17)	**BENIGN (n=7)**
SURGERY (n=24)	RIGHT HEPATECTOMY	11	3
	LEFT HEPATECTOMY	3	0
	WEDGE RESECTION	2	1
	TOTAL EXCISION	1	3

The following table shows a comparison of the complications noted in our study with the Turkish group:

	Saniye Ekinci and Ibrahim Karnak et al [82]	**ICH & HC**
Intra operative cardiac arrest due to hypovolemia	1	1
IVC injury	1	3
Bile leak	1	1
Fever	3	1
Jaundice	3	NIL
Ileus	2	NIL
Metabolic	NIL	NIL
DIC	2	NIL

The overall mortality in the Turkish study was 12% with 2 early postoperative and 1 late postoperative deaths [82] as compared to our study with a mortality rate of 16% in the immediate postoperative period (4 deaths).

Although adjuvant chemotherapy and radiotherapy have improved the prognosis of malignant tumors, complete surgical resection is still the main stay of the treatment [84][85]. Even though hepatoblastomas can be resected by primary operation, preoperative chemotherapy should preceed the operation in case of large tumors even when there is possibility of

resection [58]. This strategy helps preserve more mass of healthy hepatic tissue and decrease intraoperative and postoperative complications.

In our series out of 17 patients who underwent surgery for a malignant hepatic tumor, 8 were given preoperative chemotherapy and tumors became resectable in all cases. There was only one immediate postoperative death due to intra-operative blood loss. We attribute the decreased intra-operative blood loss to two factors: (1). Marked reduction in tumor size due to preoperative chemotherapy and (2) prior isolation of vessels supplying the area to be removed (initial isolation of the vessels at the hilum and outside the liver substance, followed by ligation and division of these structures and subsequent parenchymal transaction). But of the 9 children who were operated without preoperative chemotherapy, 3 died in the immediate postoperative period due to blood loss during surgery. This finding is akin to the observation made in the study on the effect of preoperative chemotherapy for hepatoblastoma by Minu Bajpai et al [79]. Before the era of preoperative chemotherapy, perioperative mortality was 10%. Excessive blood loss was the most common complication and was followed by cardiac arrest [80].

The high rate of resectability after chemotherapy in unresectable cases and increased survival emphasize the advantage of preoperative chemotherapy.

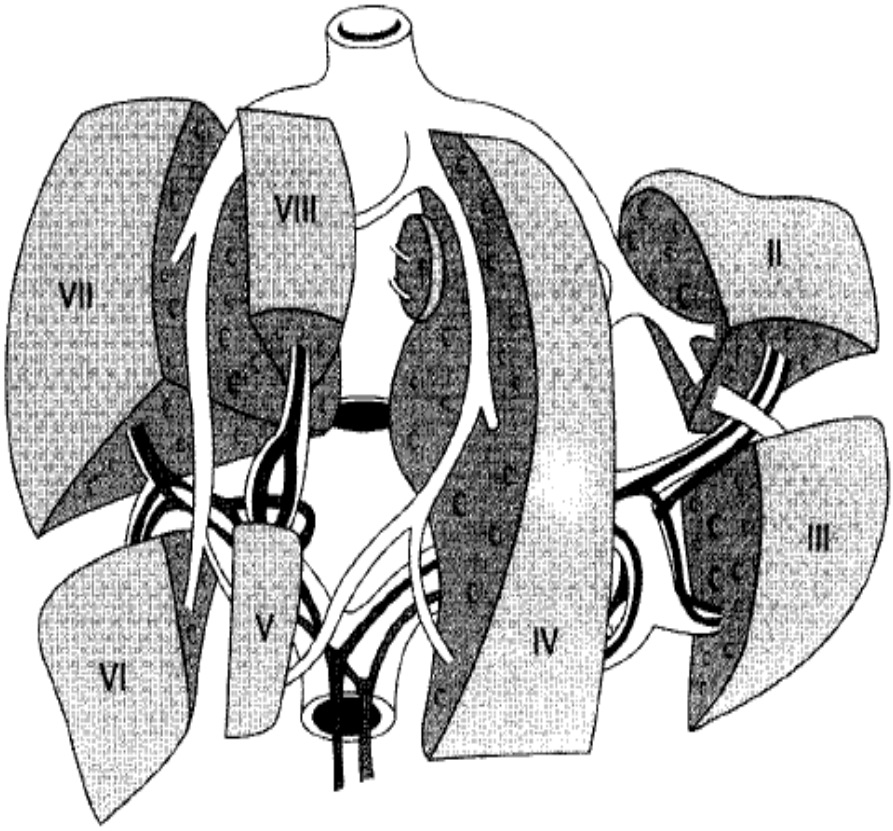
FOLLOW UP

The shortest and longest follow up in our study at ICH & HC are 2 months and 5 years respectively. The average follow up was 36 months. The primary predictor for poor prognosis in hepatoblastoma and hepatocellular carcinoma is metastatic disease. Multifocality, size, and lack of response to chemotherapy are also predictive of poor prognosis in hepatocellular carcinoma. Although metastatic disease portends a worse prognosis, some metastatic lesions have a complete response to chemotherapy. Pulmonary resection should be considered in selected patients with lung lesions that persist after chemotherapy. Following hepatic resection, most patients receive postoperative chemotherapy. Patients should be followed closely to ensure that serum AFP levels return to normal and that the neoplasm does not recur. In those patients who present with normal AFP levels, serial ultrasonography or CT can be performed to screen for recurrence.

CONCLUSION

Surgery of liver has a special point in paediatric surgical practice because Hepatic tumors are major disorders affecting children with high morbidity and mortality rates. This study covers 34 patients over a 5 year period and compares well with other established centers in India and around the world. The results are not as abysmal as previously thought of. Experience of the surgeon, familiarity to complex anatomy, strict adherence to anatomical planes, advances in anaesthesia, surgical technique, use of newer surgical tools (like CUSA, Intraoperative ultrasound, staplers etc) and chemotherapy have led to a significant improvement in the prognosis of children with hepatoblastoma. Outcomes for hepatocellular carcinoma remain poor. Anatomical resection becomes more comfortable in malignant tumors which are initially treated by preoperative chemotherapy. Liver transplantation is useful in patients with unresectable tumors.

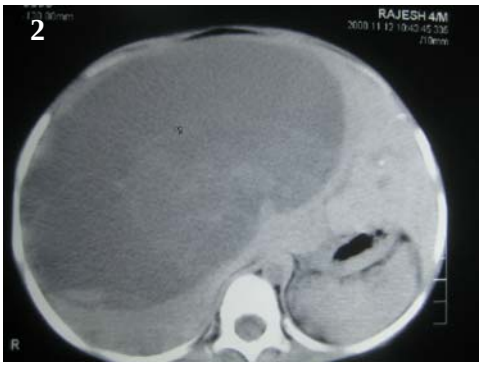
Long term goal of the centers undertaking major hepatic resections for liver malignancies in children must be pre tuned to liver transplantation, which will become the gold standard in the management of liver tumors in children in the future. Continued cooperation of multi-institutional pediatric cancer study groups will be required to achieve additional advances in the treatment of malignant liver neoplasms.



The Anatomy of the liver is divided into segemnt as described by Couinaud

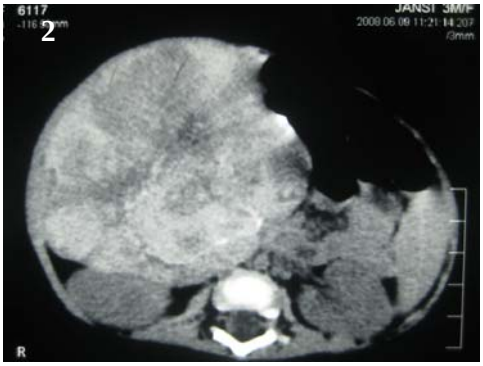
UNDIFFERENTIATED EMBRYONAL SARCOMA OF LIVER

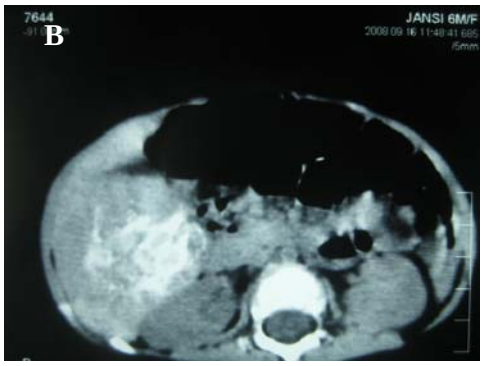
PRE CHEMOTHERAPY **POST CHEMOTHERAPY**

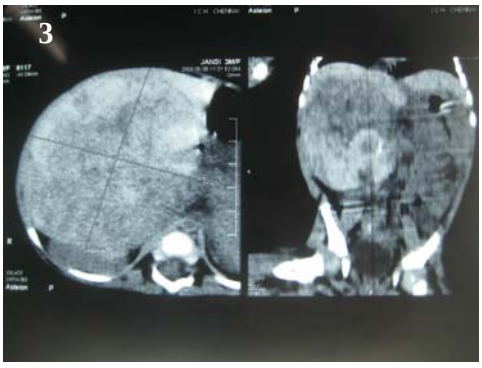


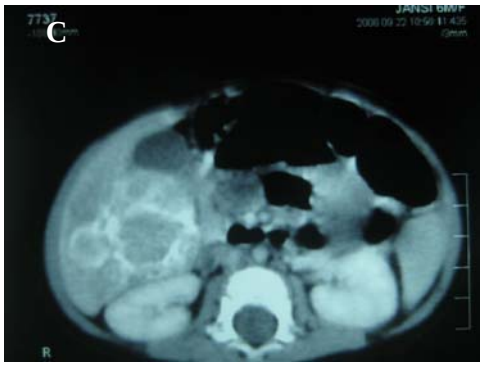
HEPATOBLASTOMA

PRE CHEMOTHERAPY **POST CHEMOTHERAPY**









HEPATOBLASTOMA RIGHT LOBE OF LIVER

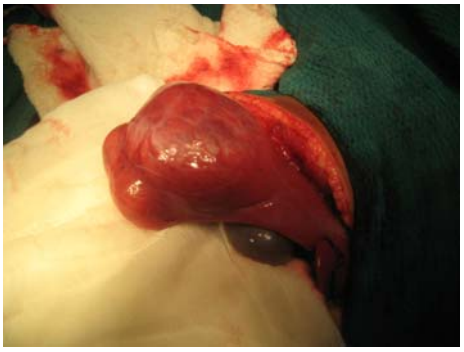
CENTRAL VENOUS ACCESS

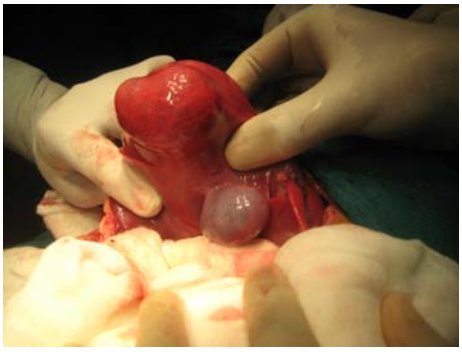
INTRA OPERATIVE PHOTOGRAPH

RIGHT HEPATECTOMY IN PROGRESS

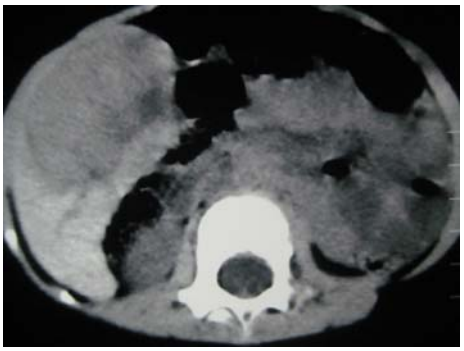
RIGHT HEPATECTOMY – RESECTED SPECIMEN

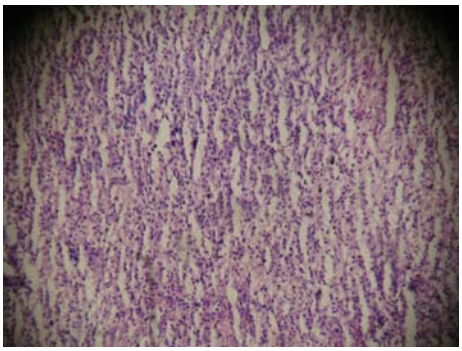
HEPATIC ADENOMA OF LIVER





INTRA OPERATIVE PHOTOGRAPH

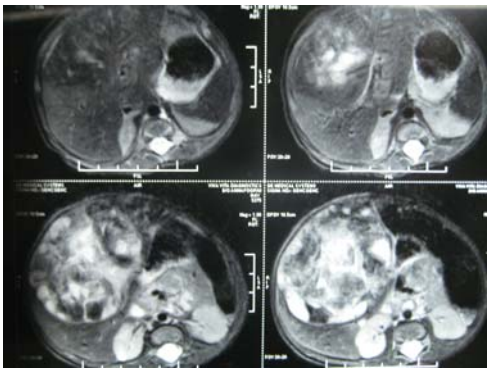




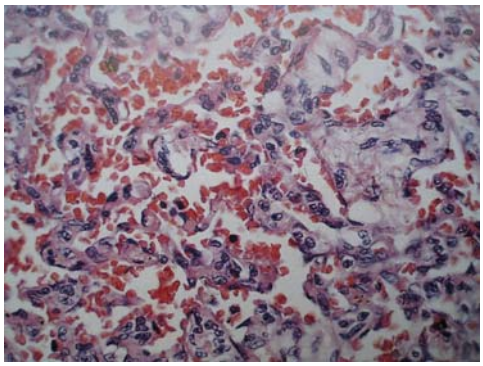
CT SCAN PICTURE **HISTOPATHOLOGY**

WEDGE RESECTION SPECIMEN AND CUT SPECIMEN OF HEPATIC ADENOMA OF LIVER

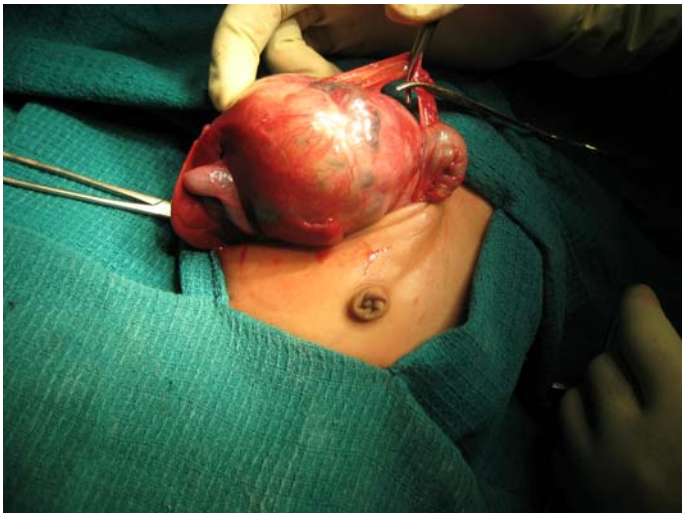
INFANTILE HEMANGIOENDOTHELIOMA OF LIVER



MAGNETIC RESONANCE IMAGING



HISTOPATHOLOGY



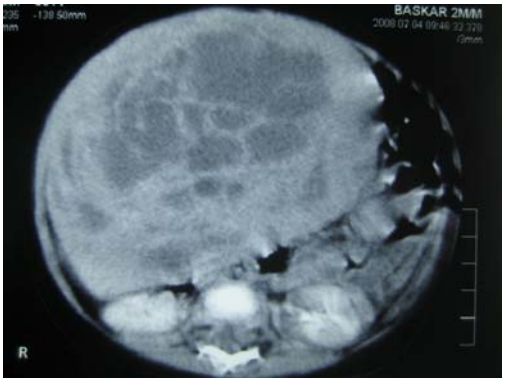
INTRA OPERATIVE PHOTOGRAPH

RESECTED SPECIMEN AND CUT SPECIMEN OF INFANTILE HEMANGIOENDOTHELIOMA OF LIVER

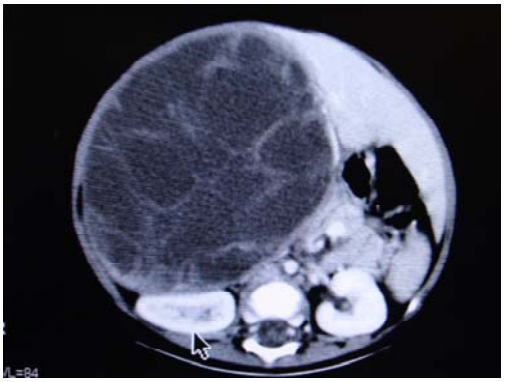
MESENCHYMAL HAMARTOMA OF LIVER

PATIENT 1
CLINICAL PHOTOGRAPH

CT SCAN SHOWING HUGE MASS IN THE LIVER



ULTRA SOUND AND CT PHOTOGRAPH OF MESENCHYMAL HAMARTOMA



PATIENT 2 - MESENCHYMAL HAMARTOMA

RECURRENT HEPATOBLASTOMA

SURVIVORS OF MALIGNANT LIVER TUMORS

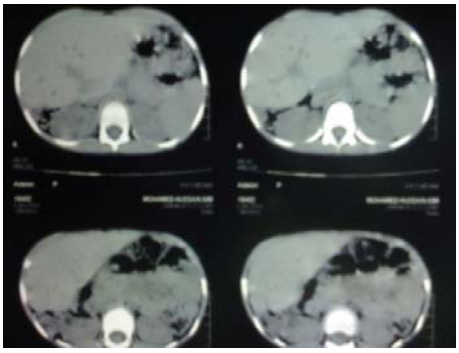
CENTRAL VENOUS ACCESS

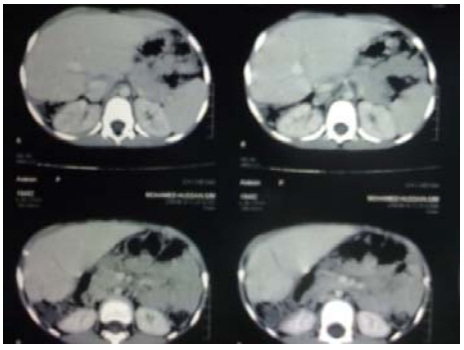
ARTERIAL PRESSURE MONITORING

COMPENSATORY HYPERTROPHY OF REMNANT LEFT LOBE OF LIVER AFTER RIGHT HEPATECTOMY

USG SHOWING MHV

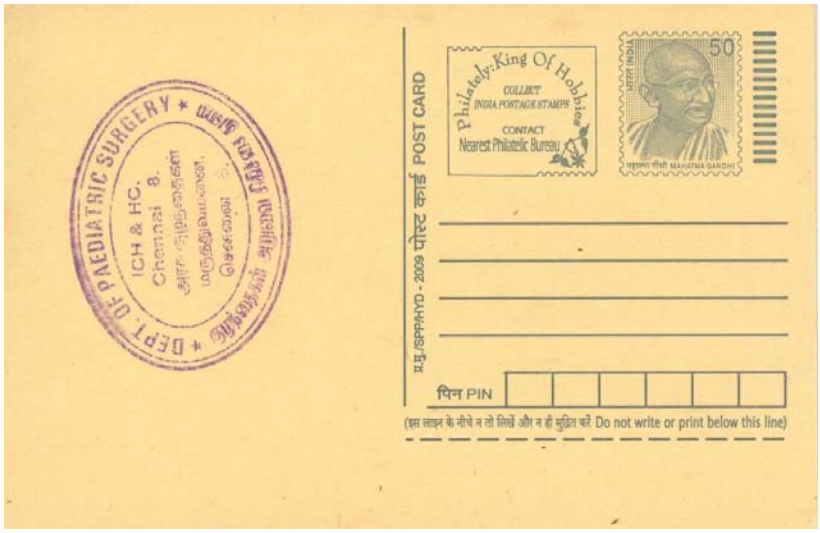
USG SHOWING MHV & LHV

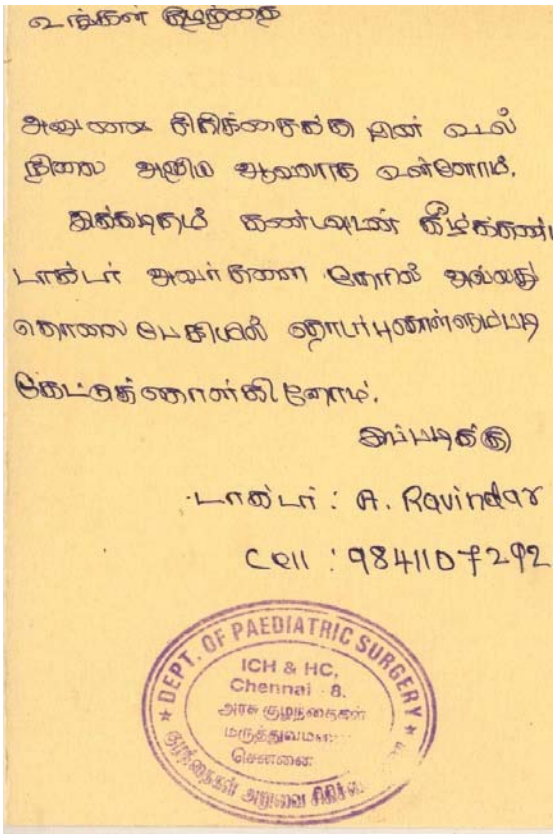


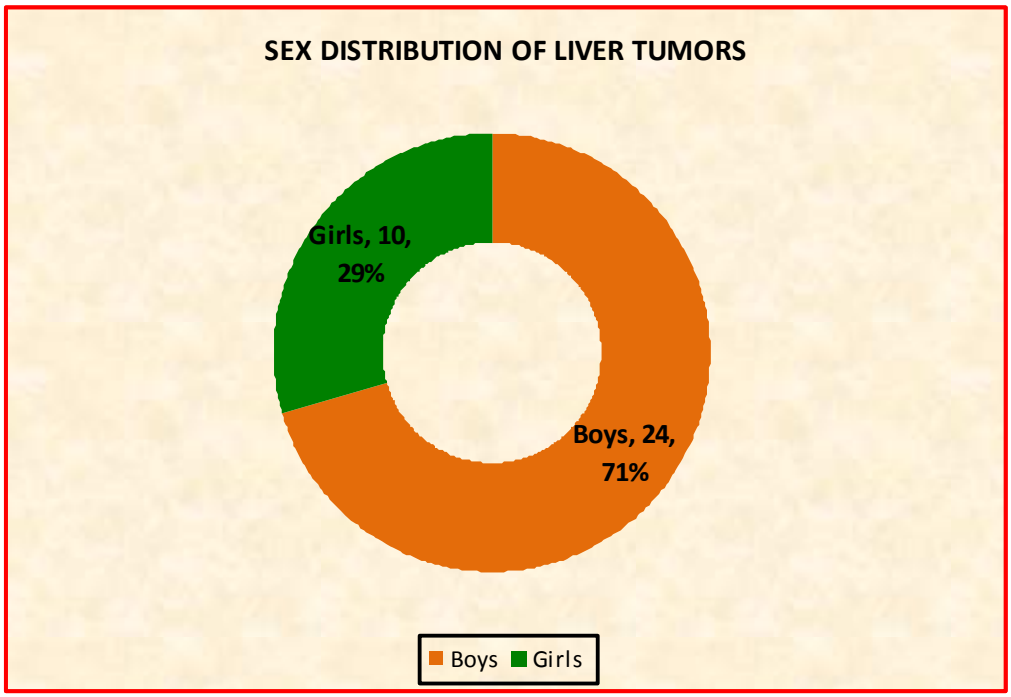


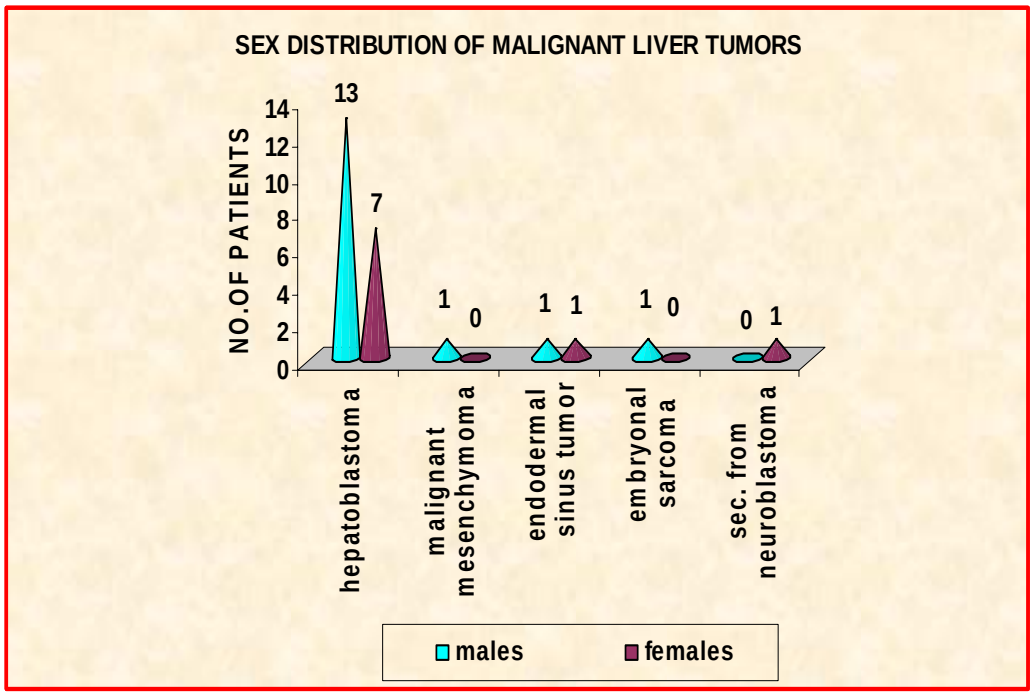
PLAIN AND CONTRAST CT SCAN SHOWING COMPENSATORY HYPERTROPHY

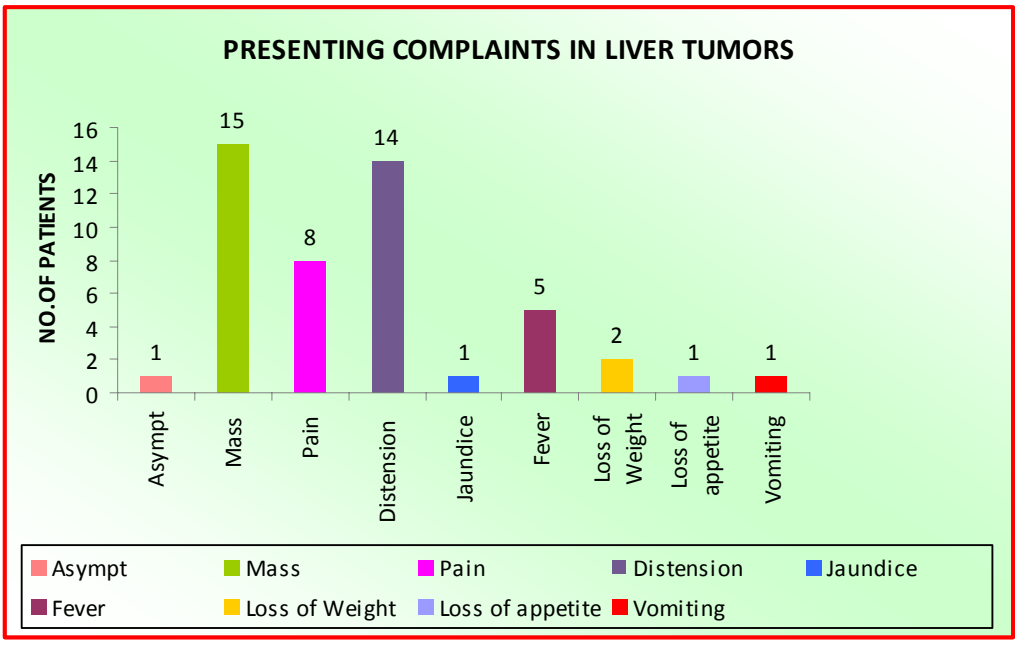
POST CARDS USED FOR FOLLOW UP

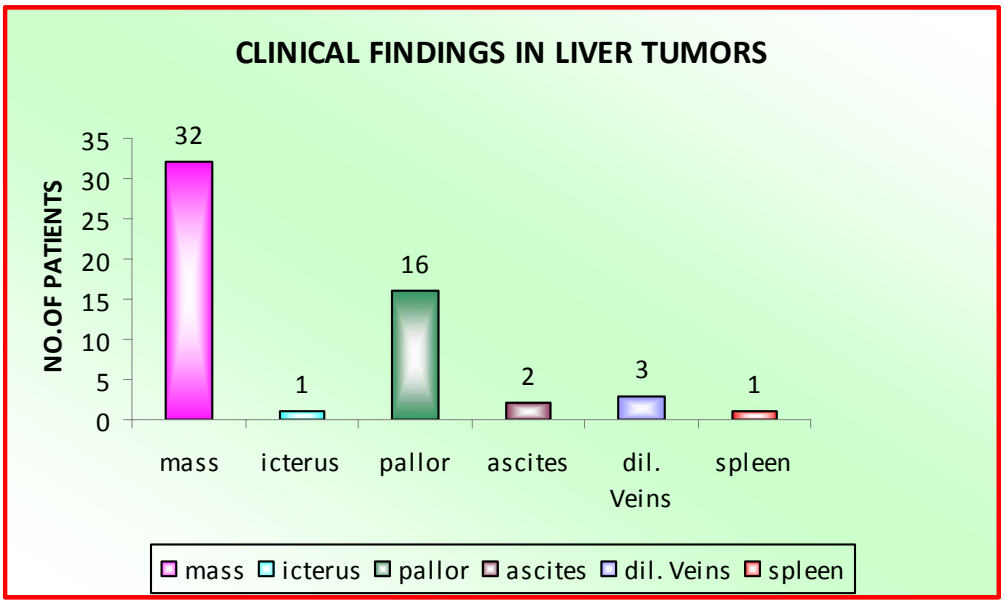


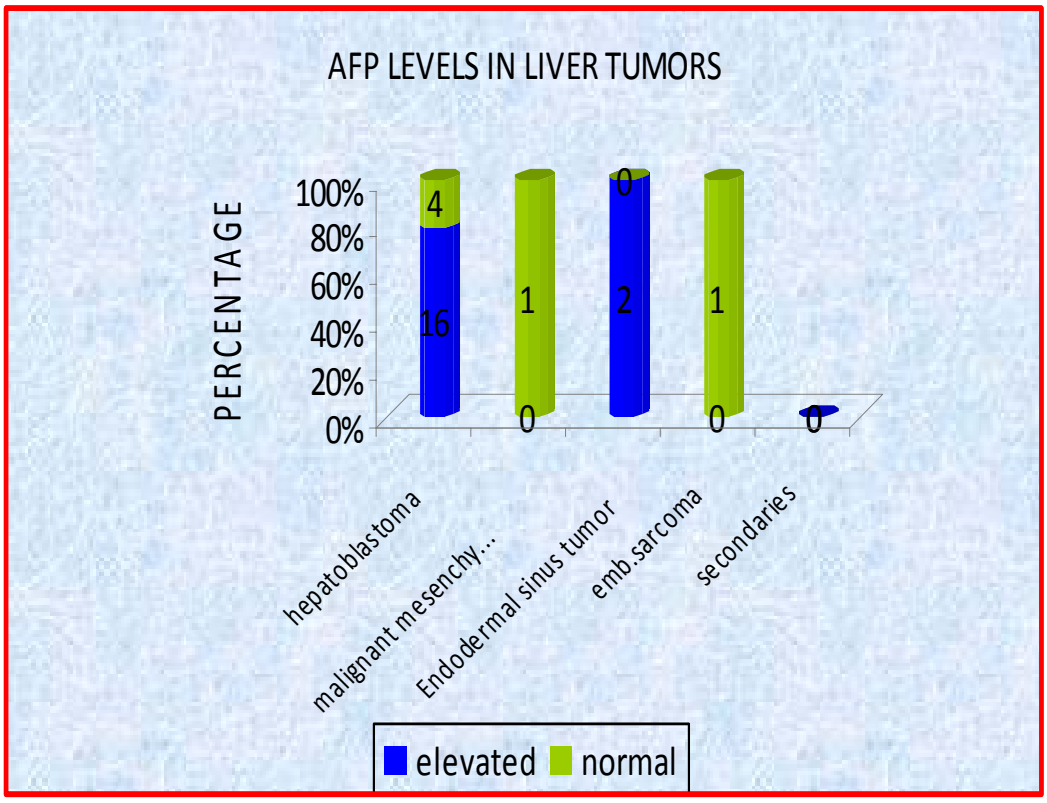


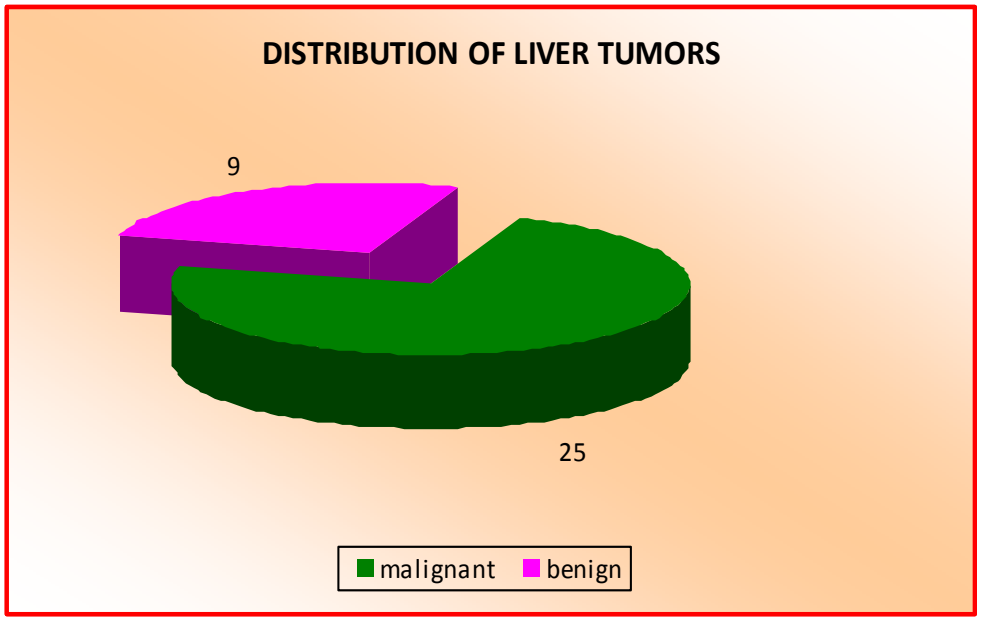

SEX DISTRIBUTION OF LIVER TUMORS
Girls, 10, 29%
Boys, 24, 71%
Boys
Girls

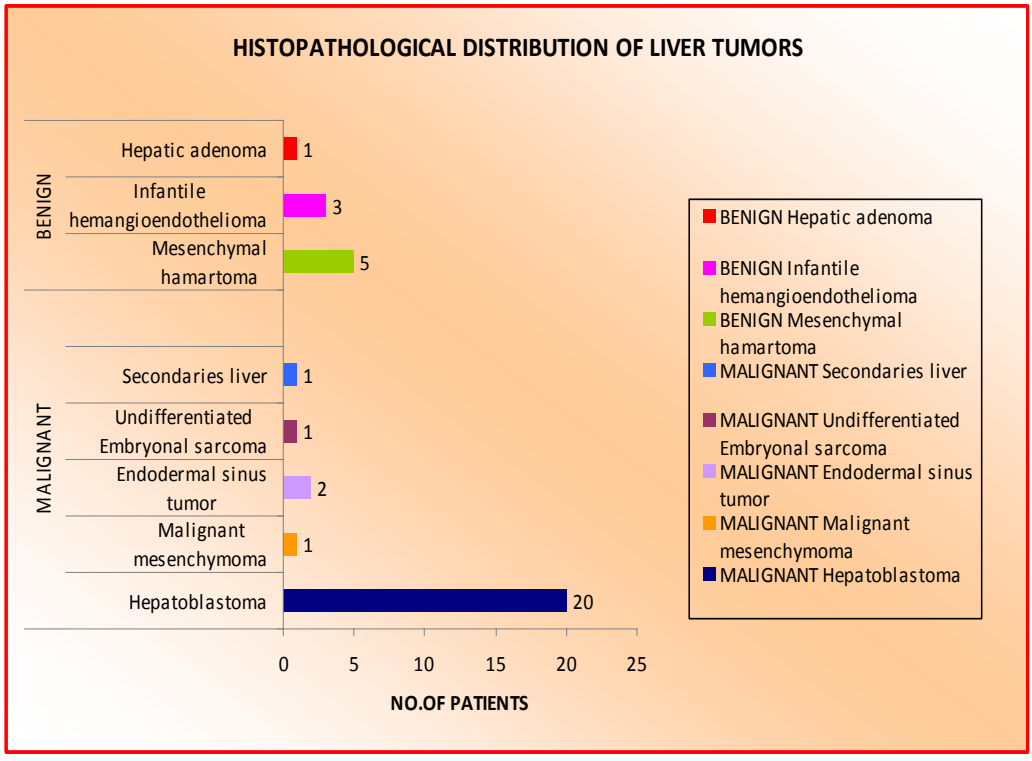

SEX DISTRIBUTION OF MALIGNANT LIVER TUMORS
NO.OF PATIENTS
14
12
10
8
6
4
2
0
13
7
1
0
1
1
1
0
0
1
hepatoblastoma
malignant mesenchymoma
endodermal sinus tumor
embryonal sarcoma
sec. from neuroblastoma
males
females

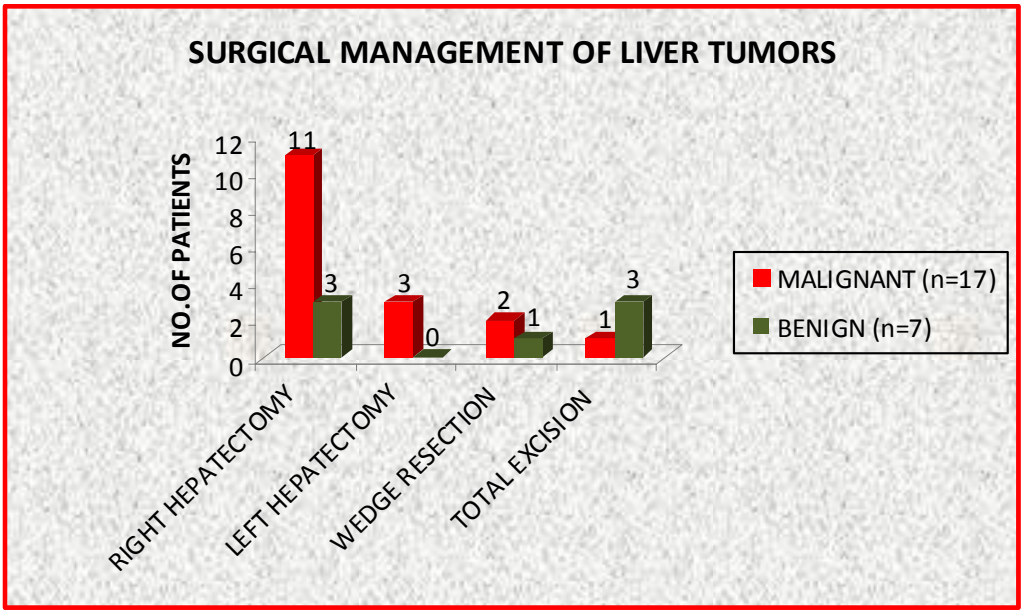

PRESENTING COMPLAINTS IN LIVER TUMORS
NO.OF PATIENTS
16
14
12
10
8
6
4
2
0
1
15
8
14
1
5
2
1
1
Asympt
Mass
Pain
Distension
Jaundice
Fever
Loss of Weight
Loss of appetite
Vomiting
Asympt
Mass
Pain
Distension
Jaundice
Fever
Loss of Weight
Loss of appetite
Vomiting

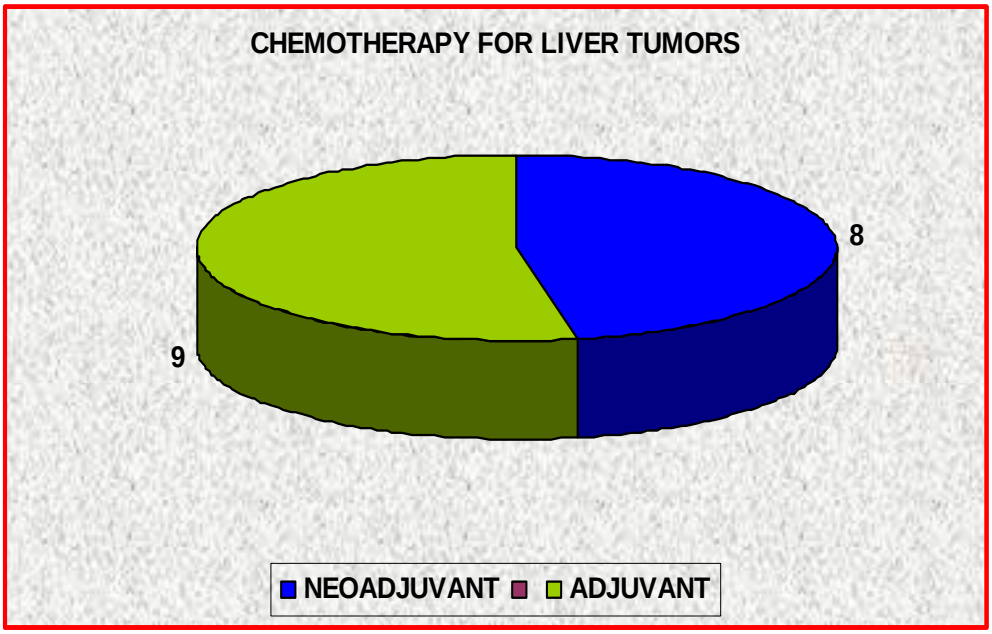

CLINICAL FINDINGS IN LIVER TUMORS
NO.OF PATIENTS
35
30
25
20
15
10
5
0
32
1
16
2
3
1
mass
icterus
pallor
ascites
dil. Veins
spleen
mass
icterus
pallor
ascites
dil. Veins
spleen

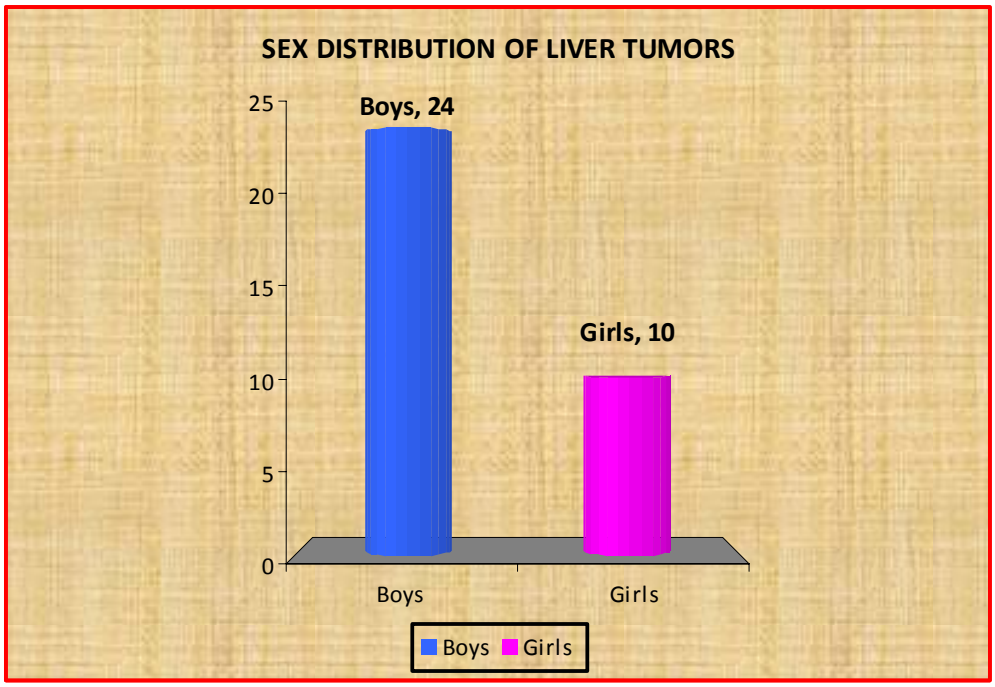

AFP LEVELS IN LIVER TUMORS
PERCENTAGE
100%
80%
60%
40%
20%
0%
4
16
1
0
0
2
1
0
0
hepatoblastoma
malignant mesenchy...
Endodermal sinus tumor
emb.sarcoma
secondaries
elevated
normal

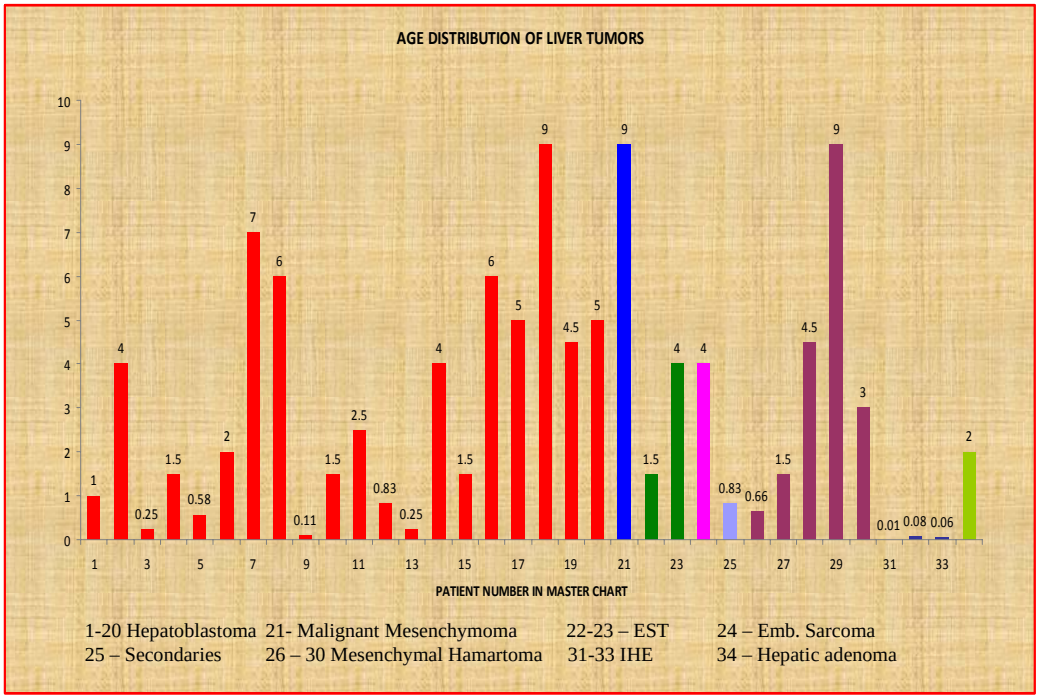

DISTRIBUTION OF LIVER TUMORS
9
25
malignant
benign


HISTOPATHOLOGICAL DISTRIBUTION OF LIVER TUMORS
BENIGN
MALIGNANT
Hepatic adenoma
Infantile hemangioendothelioma
Mesenchymal hamartoma
Secondaries liver
Undifferentiated Embryonal sarcoma
Endodermal sinus tumor
Malignant mesenchymoma
Hepatoblastoma
1
3
5
1
1
2
1
20
0
5
10
15
20
25
NO.OF PATIENTS
BENIGN Hepatic adenoma
BENIGN Infantile hemangioendothelioma
BENIGN Mesenchymal hamartoma
MALIGNANT Secondaries liver
MALIGNANT Undifferentiated Embryonal sarcoma
MALIGNANT Endodermal sinus tumor
MALIGNANT Malignant mesenchymoma
MALIGNANT Hepatoblastoma


SURGICAL MANAGEMENT OF LIVER TUMORS
NO.OF PATIENTS
12
10
8
6
4
2
0
11
3
3
0
2
1
1
3
RIGHT HEPATECTOMY
LEFT HEPATECTOMY
WEDGE RESECTION
TOTAL EXCISION
MALIGNANT (n=17)
BENIGN (n=7)


CHEMOTHERAPY FOR LIVER TUMORS
8
9
NEOADJUVANT
ADJUVANT





1-20 Hepatoblastoma 21- Malignant Mesenchymoma 22-23 – EST 24 – Emb. Sarcoma
25 – Secondaries 26 – 30 Mesenchymal Hamartoma 31-33 IHE 34 – Hepatic adenoma

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PROFORMA

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN DEPARTMENT OF PAEDIATRIC SURGERY EGMORE, CHENNAI.

LIVER TUMORS IN CHILDREN

Name **Age** **Sex** **IP No.** **Wt**

Presenting complaints

ASYMPTOMATIC	MASS ABDOMEN	ABDOMINAL PAIN	ABDOMINAL DISTENSION	JAUNDICE	OTHERS

Past history

Antenatal history

Clinical findings

MASS ABDOMEN	ICTERUS	PALLOR	ASCITES	OTHER FEATURES

Associated anomalies

HAEMANGIOMA	CONGESTIVE CARDIAC FAILURE	THROMBOCYTOPENIA	OTHERS

Investigations done

Plain x ray (CHEST/ABDOMEN)	
Usg abdomen	
BLOOD	
TUMOUR MARKERS	
CECT	
LAPAROSCOPY/BIOPSY	
Others	

HISTOPATHOLOGY

BENIGN	**MALIGNANT**

Treatment given

SURGERY	**CHEMOTHERAPY**		**OTHERS**
	NEOADJUVANT	**ADJUVANT**	

Outcome

Recovery	**Follow up**	**Complications**